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Original article

Synthesis and bioactivity evaluation of rhodanine derivatives as potential anti-bacterial agents

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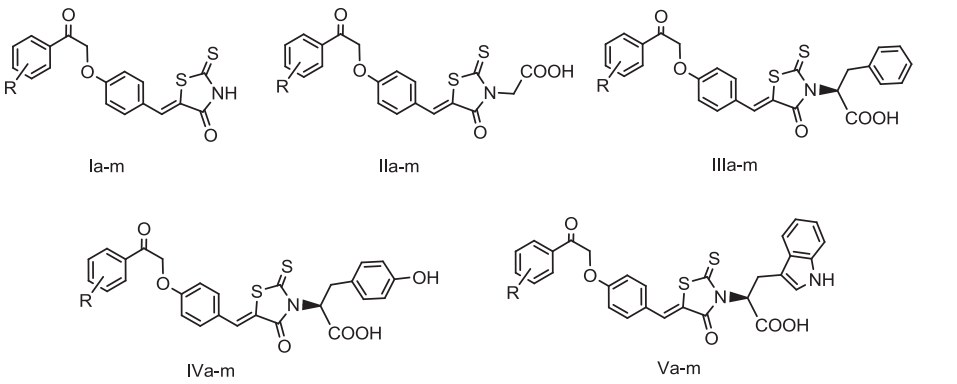
HIGHLIGHTS

- Five series of rhodanine derivatives (**I**–**V**) were synthesized.
- Some compounds showed the strongest activity with MICs of **1** μg/mL
- Compounds bearing aromatic group posses more potent activity.

GRAPHICAL ABSTRACT



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ABSTRACT

Five series of (*Z*)-5-(4-(2-oxo-2-phenylethoxy)benzylidene)-2-thioxothiazolidin-4-one derivatives (**I**–**V**) were synthesized, characterized, and evaluated for their anti-bacterial activity. Most of the synthesized compounds showed potent inhibition against several Gram-positive bacteria (including multidrug-resistant clinical isolates) with MIC values in the range of 1–32 μg/mL. Compounds **IIIi**, **Vb** and **Vc** presented the most potent activity, showing four-fold more potency than norfloxacin (MIC = 8 μg/mL and 4 μg/mL) and 64-fold more activity than oxacillin (MIC > 64 μg/mL) against *MRSA CCARM* 3167 and 3506 strains with MIC values of 1 μg/mL, and 64-fold more potency than norfloxacin (MIC > 64 μg/mL) and comparable activity to oxacillin (MIC = 1 μg/mL) against the QRSA CCARM 3505 and 3519 strains. None of the compounds exhibited any activity against the Gram-negative bacteria *Escherichia coli* 1356 at 64 μg/mL.

1. Introduction

Emerging infectious diseases and the increasing number of multi-drug resistant microbial pathogens still make the treatment of infectious diseases an important and challenging problem [1]. Therefore, there is an urgent need for the development of new anti-bacterial agents with divergent and unique structures and with a mechanism of action possibly different from that of existing anti-microbial agents [2].

Rhodanine and its derivatives have broad spectrum of biological activities as anti-bacterial [3–5], antifungal [6], antidiabetic [7], antitubercular [8,9], anti-HIV [10,11], antiparasitic [12], hypnotic [13], and anthelmintic agents [14,15]. In addition, Rhodanine

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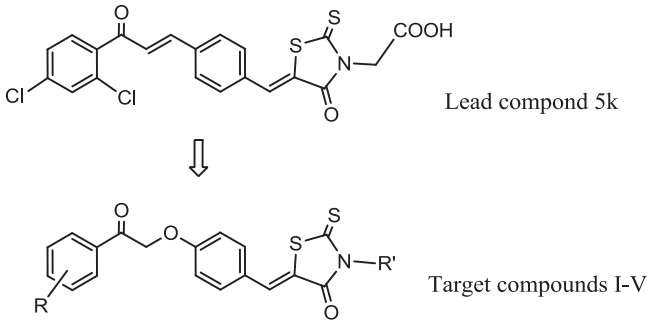


Fig. 1. Lead compound and structure-based design of the target compounds.

derivatives have been reported as anti-microbial agent against MRSA strains in the literature [16].

Previously, we reported the synthesis and anti-microbial evaluation of 2-((*E*)-4-oxo-5-(4-((*E*)-3-oxo-3-phenylprop-1-en-1-yl) benzylidene)-2-thioxothiazolidin-3-yl)acetic acid derivatives that possessed chalcone and rhodanine-3-acetic acid moieties, among which, 2-((*E*)-5-(4-((*E*)-3-(2,4-dichlorophenyl)-3-oxoprop-1-en-1-yl)benzylidene)-4-oxo-2-thioxothiazolidin-3-yl)acetic acid (**5k**) showed the strongest activity against Gram-positive strains (including multidrug-resistant clinical isolates) [17]. In the present work, as part of our ongoing research, we report the structure-based design using **5k** as the lead compound, in which the modification of **5k** was focused on reserving the rhodanine moiety, changing the chalcone moiety to a 4-(2-oxo-2-phenylethoxy) benzene and simultaneously introducing different substituents into the terminal phenyl ring. This design aimed to reduce the rigidity of chalcone moiety in **5k** expecting to get more optimized structures binding to receptor easily, consequently results in their more potent activity. Moreover, the acetic acid group on the 3-position of the rhodanine was also substituted with different aromatic amino acid side chains (including L-phenylalanine, L-tyrosine and L-tryptophan) as shown in Figs. 1 and 2. Thus, five new series of rhodanine derivatives were synthesized and a total of 65 rhodanine derivatives were characterized and screened for their anti-bacterial activities.

2. Chemistry

The synthesis of the target compounds is presented in Scheme 1. Acetophenones were used as the starting materials, which reacted with dibromohydantoin in the presence of p-toluenesulfonic acid to afford 2-bromo-1-phenylethanones (**2**). The compounds **2** were treated by 4-hydroxybenzaldehyde to provide the important intermediates 4-(2-oxo-2-phenylethoxy)benzaldehydes (**3**). The 65 target compounds (**I(a–m)-V(a–m)**) were obtained in good yields via a Knoevenagel condensation of compounds **3** and N-substituted Rhodanines, some of which were synthesized from different amino acids using the reported procedure [16]. The structures of the desired compounds were determined by IR, ^{1}H NMR, mass spectral and elemental analyses.

3. Results and discussion

3.1. Anti-bacterial activity

The *in vitro* anti-bacterial activity was evaluated using a 96-well microtiter plate and a serial dilution method to obtain the Minimum Inhibitory Concentration (MIC) with different strains including multidrug-resistant clinical isolates. Oxacillin and norfloxacin were used as positive controls.

In a preliminary *in vitro* assay, all the synthesized compounds **I(a–m)**–**V(a–m)** were screened for their activity against three Gram-positive strains (*Staphylococcus aureus RN* 4220, *S. aureus KCTC* 209 and *S. aureus KCTC* 503) and one Gram-negative strain (*Escherichia coli* 1356). The results indicated that most of the synthesized compounds showed potent inhibition against three Gram-positive bacteria with MIC values in the range of 1–32 μg/mL. Among the tested compounds in the five series, the compounds in series **III** and **V** showed excellent inhibition against the three Gram-positive strains (*S. aureus RN* 4220, *S. aureus KCTC* 209 and *S. aureus KCTC* 503), with MIC values in the range of 1–8 μg/mL. In particular, compound **Vc** (MIC = 1 μg/mL) had a 2-fold more potent activity than the positive control norfloxacin (MIC = 2 μg/mL), and comparable activity to the positive control oxacillin (MIC = 1 μg/mL) against the Gram-positive strains. Compounds in series **IV** exhibited good activity against the Gram-positive strains with MIC values ranging from 4 to 32 μg/mL. Compounds in series **I** and **II** displayed moderate to good inhibition against *S. aureus KCTC* 209 and *S. aureus KCTC* 503 (MIC = 8–32 μg/mL), only a few of them exhibited moderate activity against *S. aureus RN* 4220 (MIC = 16 or 32 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 in all five series were also evaluated for their inhibitory activity against several clinical isolates of multidrug-resistant Gram-positive bacterial strains (methicillin-resistant *S. aureus* (*MRSA CCARM* 3167 and *MRSA CCARM* 3506) and quinolone-resistant *S. aureus* (*QRSA CCARM* 3505 and *QRSA CCARM*

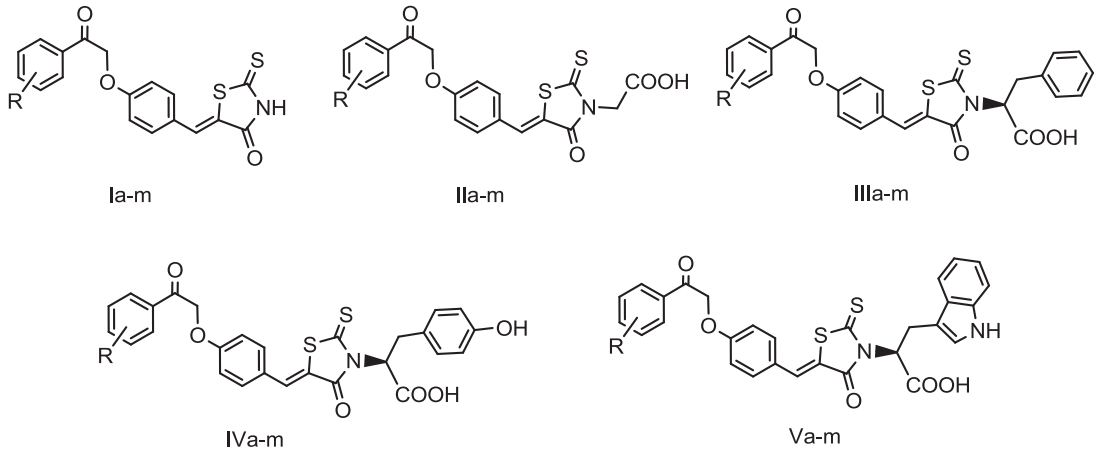
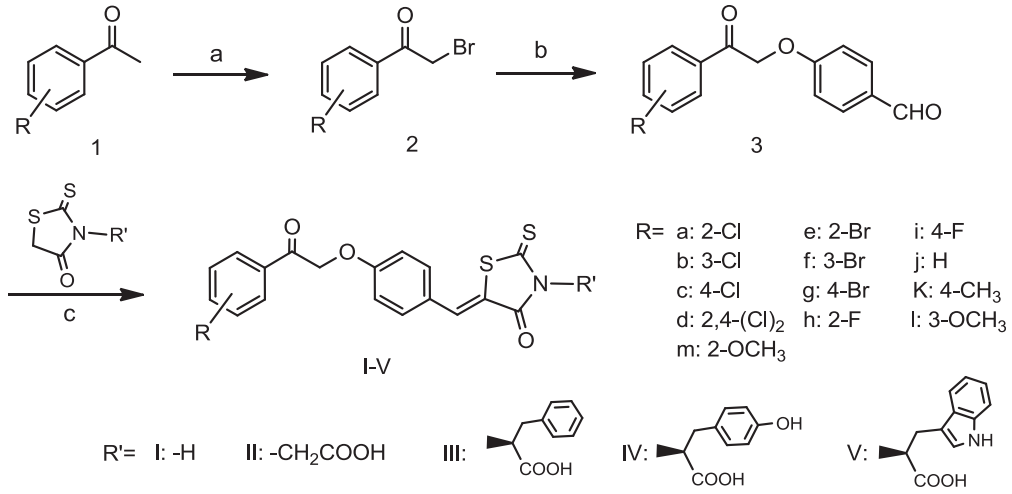


Fig. 2. Structures of the target compounds **I**–**V**.



Scheme 1. Synthetic scheme for the synthesis of compounds **I**–**V**.

3519)). The MIC values of the compounds differed greatly, ranging from 1 to 32 μg/mL. Compounds in series **I** and **II** exhibited moderate activity, most of which with MICs of 16 or 32 μg/mL against *MRSA CCARM* (3167 and 3506) and *QRSA CCARM* (3505 and 3519) strains. Only compound **Ia** displayed potent activity against *MRSA CCARM* 3506 (MIC = 4 μg/mL), and compound **IId** showed good activity against four multidrug-resistant Gram-positive bacterial strains (MIC = 8 μg/mL). As shown in Table 2, against the four multidrug-resistant Gram-positive bacterial strains, compounds in series **IV** presented the high activity with MIC values of 8–32 μg/mL, making them slightly less active than compounds in series **III** and **V** (MIC = 1–8 μg/mL), but much more potent than compounds in series **I** and **II**. Most compounds in series **III** and **V** presented comparable or much more potent activities than norfloxacin and oxacillin against *MRSA CCARM* (3167, 3506) strains and *QRSA CCARM* (3505, 3519) strains. Among them, compounds **IIIi**, **Vb** and **Vc** were the most potent, with MIC values of 1 μg/mL, eight or four-fold more potent than norfloxacin (MIC = 8 μg/mL and 4 μg/mL) and 64-fold more active than oxacillin (MIC > 64 μg/mL) against *MRSA CCARM* 3167 and 3506 strains. And they were 64-fold more potent than norfloxacin (MIC > 64 μg/mL) and had comparable activity to oxacillin (MIC = 1 μg/mL) against the QRSA CCARM 3505 and 3519 strains. Compared to the leading compound **5k**, the inhibitory activity of compounds **IIIi**, **Vb** and **Vc** is more potent than 5k (MIC = 2 μg/mL).

The order of potency of the five series of compounds was **V** > III > **IV** > **II** > **I**, from which it could be concluded that for these rhodanine derivatives, a free carboxyl group seems to be necessary for the anti-bacterial activity against Gram-positive strains. As well, the compounds bearing aromatic groups on the 3-position of the rhodanine (**III**–**V**) possess much more potent activity compared with the compounds in series **I** and **II**. A comparison of the compounds in series **III** with those in series **IV** indicates that the introduction of a hydroxy group to the phenyl ring lowers the antimicrobial activity. The above results agreed with the hypothesis of D. Hardej that the phenylalanine or other hydrophobic amino acid substituents at the N3-position would increase the likelihood of penetration through the bacterial cell wall and therefore potentially

Table 1
Inhibitory activity (MIC[a], μg/mL) of compounds **III**–**V** against bacteria.

Compd.	Gram-positive strains			Gram-negative strains	Compd.	Gram-positive strains			Gram-negative strains
	S. aureus			*E. coli*		*S. aureus*			*E. coli*
	4220	209	503	1356		4220	209	503	1356
III-a	8	8	8	>64	**IV-i**	8	8	8	>64
III-b	8	4	4	>64	**IV-j**	32	32	32	>64
III-c	4	4	8	>64	**IV-k**	32	4	8	>64
III-d	8	8	8	>64	**IV-l**	32	8	8	>64
III-e	8	4	8	>64	**IV-m**	32	8	8	>64
III-f	4	4	4	>64	**V-a**	8	4	4	>64
III-g	8	8	8	>64	**V-b**	8	4	4	>64
III-h	8	4	8	>64	**V-c**	**1**	**1**	**1**	>64
IIIi	4	4	4	>64	**V-d**	8	4	8	>64
III-j	8	4	8	>64	**V-e**	8	4	4	>64
III-k	8	8	8	>64	**V-f**	4	2	4	>64
III-l	8	8	8	>64	**V-g**	8	4	4	>64
III-m	4	4	4	>64	**V-h**	8	8	8	>64
IV-a	16	16	8	>64	**V-i**	4	4	4	>64
IV-b	8	8	8	>64	**V-j**	8	8	8	>64
IV-c	16	8	8	>64	**V-k**	8	4	4	>64
IV-d	8	4	4	>64	**V-l**	8	8	8	>64
IV-e	32	16	16	>64	**V-m**	8	8	8	>64
IV-f	8	8	8	>64	**5k**	2	2	2	>64
IV-g	8	4	4	>64	Norfloxacin	2	2	2	16
IV-h	32	8	16	>64	Oxacillin	1	1	1	>64

[a] The anti-bacterial testing were carried out three times, and the MICs are average of them.

Table 2
Inhibitory activity (MIC[a], μg/mL) of compounds **III**–**V** against clinical isolates of multidrug-resistant Gram-positive strains.

Compd.	Gram-positive strains				Compd.	Gram-positive strains			
	MRSA		*QRSA*			*MRSA*		*QRSA*	
	3167	3506	3505	3519		3167	3506	3505	3519
III-a	4	4	4	4	**IV-i**	8	8	8	8
III-b	4	4	4	4	**IV-j**	32	32	32	32
III-c	4	4	4	4	**IV-k**	16	16	16	16
III-d	8	8	8	8	**IV-l**	8	16	8	16
III-e	4	8	4	8	**IV-m**	8	8	8	8
III-f	4	4	4	4	**V-a**	8	8	8	8
III-g	4	8	4	8	**V-b**	**1**	**1**	**1**	**1**
III-h	4	4	4	4	**V-c**	**1**	**1**	**1**	**1**
IIIi	**1**	**1**	**1**	**1**	**V-d**	4	8	4	8
III-j	8	4	8	4	**V-e**	4	8	4	8
III-k	4	8	4	8	**V-f**	4	4	4	4
III-l	8	8	8	8	**V-g**	8	8	8	8
III-m	4	4	4	4	**V-h**	8	8	8	8
IV-a	8	16	8	16	**V-i**	4	4	4	4
IV-b	8	8	8	8	**V-j**	8	8	8	8
IV-c	8	16	8	16	**V-k**	4	8	4	8
IV-d	8	8	8	8	**V-l**	8	8	8	8
IV-e	16	32	16	32	**V-m**	8	8	8	8
IV-f	8	8	8	8	**5k**	2	2	2	2
IV-g	8	8	8	8	Norfloxacin	8	4	>64	>64
IV-h	16	16	16	16	Oxacillin	>64	>64	1	1

[a] The anti-bacterial testing were carried out three times, and the MICs are average of them.

improve their anti-bacterial activity of the compound [16]. No clear pattern was found for the structure activity relationship between the anti-bacterial activity and the position and physicochemical property of the different substituents on the phenyl ring.

4. Conclusion

Based on our previous work, we synthesized five new series of rhodanine derivatives (**I**–**V**) and evaluated them for their anti-bacterial activities against Gram-positive and Gram-negative bacteria. Most of the compounds showed good anti-bacterial activities against Gram-positive bacteria as well as multidrug-resistant strains of clinical isolates. Compounds in series **III** and **V** were found to have the most potent inhibitory capacity, and the compounds **IIIi**, **Vb** and **Vc** were found to possess more potent activity than the standard drugs oxacillin and norfloxacin against all the tested multidrug-resistant clinical isolates with MICs of 1 μg/mL. Currently, the mechanism of action of the compounds tested in this study is unknown. Most synthesized compounds did produce a bactericidal action on selected Gram-positive bacterial strains (including multidrug-resistant clinical isolates). Typically, antibiotics can produce a bactericidal effect by inhibiting cell wall or DNA synthesis. Thus, it is possible that the bactericidal compounds in this study could act via these mechanisms, although this remains to be proven. These results provide the basis for further studies, especially in relation to the search for new derivatives with better anti-microbial activities against methicillin-resistant and quinolone-resistant *S. aureus*.

5. Experimental protocols

5.1. Chemistry

Melting points were determined in open capillary tubes 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 spectra were measured on a Bruker AV-300 spectrometer using TMS as the internal standard. Mass spectra were measured on an HP1100LC (Agilent Technologies, Santa Clara, CA, USA). Elemental analyses for C, H and N were within ±0.4% of the theoretical values and were carried out on a 204Q CHN Rapid Analyzer (Perkin–Elmer, Waltham, MA, USA). The major chemicals were purchased from Sigma–Aldrich (St. Louis, MO, USA) and Fluka Companies (Milwaukee, MI, USA).

5.2. General procedure for the preparation of compounds **2**

To a solution of the appropriate acetophenone **1** and *p*-toluenesulfonic acid (15 mmol) in dry methanol (20 mL), dibromohydantoin (15 mmol), diluted in methanol (20 mL) was added dropwise and the mixture was stirred for 8 h at 30 °C. After the completion of the reaction, excess solvent was removed under reduced pressure. Ice water was added to the residue. The precipitated solid was filtered, and washed with ethanol. The resulting crude solid was directly used in the next step without purification.

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

To a solution of 4-hydroxybenzaldehyde (10 mmol) and K_2CO_3 (20 mmol) in dry acetone (20 mL), the corresponding substituted 2-bromo-1-phenylethanone (10 mmol) was added and the mixture was stirred overnight at the room temperature. After the completion of the reaction, excess solvent was removed under reduced pressure. The compound was extracted into dichloromethane, concentrated and purified by column chromatography (dichloromethane: petroleum ether = 50: 1).

5.4. General procedure for the preparation of compounds **I**

A mixture of **3** (3 mmol), 2-thioxothiazolidin-4-one (3 mmol), 10 drops glacial acetic acid and 10 drops piperidine in ethanol (20 mL) was refluxed for 4 h. After cooling, a precipitate was obtained by filtration, which was further recrystallized from ethanol to provide a yellow solid **Ia**–**m**.

5.4.1. (Z)-5-(4-(2-(2-chlorophenyl)-2-oxoethoxy) benzylidene)-2-thioxothiazolidin-4-one (***I-a***)

Yield 87%; m.p. 152–154 °C. IR (KBr) cm^{-1}: 3210 (NH), 1675 (C=O). ^{1}H NMR (DMSO-d_6, 300 MHz, ppm): δ 5.07 (s, 2H, COC$\underline{H}_2$), 7.77 (s, 1H, C$\underline{H}$), 6.91–7.91 (m, 8H, Ar–$\underline{H}$), 10.48 (s, 1H, N$\underline{H}$). MS *m/z* 390 (M + 1). Anal. Calcd. for $C_{18}H_{12}ClNO_3S_2$: C, 55.45; H, 3.10; N, 3.59. Found: C, 55.35; H, 3.16; N, 3.71.

5.4.2. (Z)-5-(4-(2-(3-chlorophenyl)-2-oxoethoxy) benzylidene)-2-thioxothiazolidin-4-one (***I-b***)

Yield 89%; m.p. 214–216 °C. IR (KBr) cm^{-1}: 3217 (NH), 1682 (C=O). ^{1}H NMR (DMSO-d_6, 300 MHz, ppm): δ 5.24 (s, 2H, COC$\underline{H}_2$), 7.76 (s, 1H, C$\underline{H}$), 6.91–8.09 (m, 8H, Ar–$\underline{H}$), 10.46 (s, 1H, N$\underline{H}$). MS *m/z* 390 (M + 1). Anal. Calcd. for $C_{18}H_{12}ClNO_3S_2$: C, 55.45; H, 3.10; N, 3.59. Found: C, 55.74; H, 3.27; N, 3.76.

5.4.3. (Z)-5-(4-(2-(4-chlorophenyl)-2-oxoethoxy) benzylidene)-2-thioxothiazolidin-4-one (***I-c***)

Yield 85%; m.p.178–180 °C. IR (KBr) cm^{-1}: 3214 (NH), 1680 (C=O). ^{1}H NMR (DMSO-d_6, 300 MHz, ppm): δ 5.23 (s, 2H, COC$\underline{H}_2$), 7.76 (s, 1H, C$\underline{H}$), 6.91–8.09 (m, 8H, Ar–$\underline{H}$), 10.46 (s, 1H, N$\underline{H}$). MS *m/z* 390 (M + 1). Anal. Calcd. for $C_{18}H_{12}ClNO_3S_2$: C, 55.45; H, 3.10; N, 3.59. Found: C, 55.36; H, 3.18; N, 3.72.

5.4.4. (Z)-5-(4-(2-(2,4-dichlorophenyl)-2-oxoethoxy)benzylidene)-2-thioxothiazolidin-4-one (***I-d***)

Yield 86%; m.p. 140–142 °C. IR (KBr) cm^{-1}: 3216 (NH), 1684 (C=O). ^{1}H NMR (DMSO-d_6, 300 MHz, ppm): δ 5.70 (s, 2H, COC$\underline{H}_2$), 7.74

(s, 1H, CH), 6.89–7.74 (m, 8H, Ar–H), 10.37 (s, 1H, NH). MS *m/z* 424 (M + 1). Anal. Calcd. for $C_{18}H_{11}Cl_2NO_3S_2$: C, 50.95; H, 2.61; N, 3.30. Found: C, 51.22; H, 2.75; N, 3.52.

*5.4.5. (Z)-5-(4-(2-(2-bromophenyl)-2-oxoethoxy)benzylidene)-2-thioxothiazolidin-4-one (**I-e**)*

Yield 87%; m.p. 144–146 °C. IR (KBr) cm^{-1}: 3220 (NH), 1686 (C=O). ^1H NMR (DMSO-d_6, 300 MHz, ppm): δ 5.05 (s, 2H, $COCH_2$), 7.76 (s, 1H, CH), 6.91–7.87 (m, 8H, Ar–H), 10.47 (s, 1H, NH). MS *m/z* 434 (M + 1). Anal. Calcd. for $C_{18}H_{12}BrNO_3S_2$: C, 49.78; H, 2.78; N, 3.22. Found: C, 49.53; H, 2.94; N, 3.06.

*5.4.6. (Z)-5-(4-(2-(3-bromophenyl)-2-oxoethoxy)benzylidene)-2-thioxothiazolidin-4-one (**I-f**)*

Yield 82%; m.p. 210–212 °C. IR (KBr) cm^{-1}: 3218 (NH), 1685 (C=O). ^1H NMR (DMSO-d_6, 300 MHz, ppm): δ 5.06 (s, 2H, $COCH_2$), 7.76 (s, 1H, CH), 6.92–8.13 (m, 8H, Ar–H), 10.46 (s, 1H, NH). MS *m/z* 434 (M + 1). Anal. Calcd. for $C_{18}H_{12}BrNO_3S_2$: C, 49.78; H, 2.78; N, 3.22. Found: C, 49.99; H, 2.84; N, 3.36.

*5.4.7. (Z)-5-(4-(2-(3-bromophenyl)-2-oxoethoxy)benzylidene)-2-thioxothiazolidin-4- one (**I-g**)*

Yield 84%; m.p. 177–178 °C. IR (KBr) cm^{-1}: 3217 (NH), 1683 (C=O). ^1H NMR (DMSO-d_6, 300 MHz, ppm): δ 5.22 (s, 2H, $COCH_2$), 7.75 (s, 1H, CH), 6.90–8.01 (m, 8H, Ar–H), 10.46 (s, 1H, NH). MS *m/z* 434 (M + 1). Anal. Calcd. for $C_{18}H_{12}BrNO_3S_2$: C, 49.78; H, 2.78; N, 3.22. Found: C, 49.53; H, 2.93; N, 3.40.

*5.4.8. (Z)-5-(4-(2-(2-fluorophenyl)-2-oxoethoxy)benzylidene)-2-thioxothiazolidin-4-one (**I-h**)*

Yield 86%; m.p. 170–171 °C. IR (KBr) cm^{-1}: 3213 (NH), 1672 (C=O). ^1H NMR (DMSO-d_6, 300 MHz, ppm): δ 5.11 (s, 2H, $COCH_2$), 7.76 (s, 1H, CH), 6.91–7.96 (m, 8H, Ar–H), 10.46 (s, 1H, NH). MS *m/z* 374 (M + 1). Anal. Calcd. for $C_{18}H_{12}FNO_3S_2$: C, 57.90; H, 3.24; N, 3.75. Found: C, 58.17; H, 3.36; N, 3.48.

*5.4.9. (Z)-5-(4-(2-(4-fluorophenyl)-2-oxoethoxy)benzylidene)-2-thioxothiazolidin-4-one (**I-i**)*

Yield 81%; m.p. 245–246 °C. IR (KBr) cm^{-1}: 3215 (NH), 1676 (C=O). ^1H NMR (DMSO-d_6, 300 MHz, ppm): δ 5.70 (s, 2H, $COCH_2$), 7.61 (s, 1H, CH), 7.12–8.13 (m, 8H, Ar–H), 13.78 (s, 1H, NH). MS *m/z* 374 (M + 1). Anal. Calcd. for $C_{18}H_{12}FNO_3S_2$: C, 57.90; H, 3.24; F, 5.09; N, 3.75. Found: C, 58.08; H, 3.31; N, 3.53.

*5.4.10. (Z)-5-(4-(2-oxo-2-phenylethoxy)benzylidene)-2-thioxothiazolidin-4-one (**I-j**)*

Yield 87%; m.p. 194–196 °C. IR (KBr) cm^{-1}: 3210 (NH), 1672 (C=O). ^1H NMR (DMSO-d_6, 300 MHz, ppm): δ 5.25 (s, 2H, $COCH_2$), 7.76 (s, 1H, CH), 6.91–8.08 (m, 9H, Ar–H), 10.46 (s, 1H, NH). MS *m/z* 356 (M + 1). Anal. Calcd. for $C_{18}H_{13}NO_3S_2$: C, 60.83; H, 3.69; N, 3.94. Found: C, 60.67; H, 3.74; N, 4.09.

*5.4.11. (Z)-5-(4-(2-oxo-2-(p-tolyl)ethoxy)benzylidene)-2-thioxothiazolidin-4-one (**I-k**)*

Yield 83%; m.p. 247–249 °C. IR (KBr) cm^{-1}: 3217 (NH), 1685 (C=O). ^1H NMR (DMSO-d_6, 300 MHz, ppm): δ 2.49 (s, 3H, CH_3), 5.21 (s, 2H, $COCH_2$), 7.75 (s, 1H, CH), 6.90–8.22 (m, 8H, Ar–H), 10.45 (s, 1H, NH). MS *m/z* 370 (M + 1). Anal. Calcd. for $C_{19}H_{15}NO_3S_2$: C, 61.77; H, 4.09; N, 3.79. Found: C, 61.95; H, 4.02; N, 3.84.

*5.4.12. (Z)-5-(4-(2-(3-methoxyphenyl)-2-oxoethoxy)benzylidene)-2-thioxothiazolidin-4-one (**I-l**)*

Yield 88%; m.p. 193–195 °C. IR (KBr) cm^{-1}: 3221 (NH), 1687 (C=O). ^1H NMR (DMSO-d_6, 300 MHz, ppm): δ 3.84 (s, 3H, OCH_3), 5.23 (s, 2H, $COCH_2$), 7.76 (s, 1H, CH), 6.91–7.76 (m, 8H, Ar–H), 10.46 (s, 1H, NH). MS *m/z* 386 (M + 1). Anal. Calcd. for $C_{19}H_{15}NO_4S_2$: C, 59.20; H, 3.92; N, 3.63. Found: C, 59.36; H, 4.15; N, 3.51.

*5.4.13. (Z)-5-(4-(2-(4-methoxyphenyl)-2-oxoethoxy)benzylidene)-2-thioxothiazolidin-4-one (**I-m**)*

Yield 87%; m.p.190–192 °C. IR (KBr) cm^{-1}: 3225 (NH), 1689 (C=O). ^1H NMR (DMSO-d_6, 300 MHz, ppm): δ 3.86 (s, 3H, OCH_3), 5.19 (s, 2H, $COCH_2$), 7.75 (s, 1H, CH), 6.91–8.06 (m, 8H, Ar–H), 10.46 (s, 1H, NH). MS *m/z* 386 (M + 1). Anal. Calcd. for $C_{19}H_{15}NO_4S_2$: C, 59.20; H, 3.92; N, 3.63. Found: C, 59.04; H, 3.98; N, 3.53.

*5.5. General procedure for the preparation of compounds **II***

A mixture of **3** (3 mmol), 2-(4-oxo-2-thioxothiazolidin-3-yl) acetic acid (3 mmol), 10 drops glacial acetic acid and 10 drops piperidine in ethanol (20 mL) was refluxed for 4 h. After cooling, a precipitate was obtained by filtration, which was further recrystallized from ethanol to provide a yellow solid **IIa-m**.

*5.5.1. (Z)-2-(5-(4-(2-(2-chlorophenyl)-2-oxoethoxy)benzylidene)-4-oxo-2-thioxothia-zolidin-3-yl)acetic acid(**II-a**)*

Yield 91%; m.p. 152–154 °C. IR (KBr) cm^{-1}: 3413 (OH), 1702 (C=O). ^1H NMR (DMSO-d_6, 300 MHz, ppm): δ 4.35 (s, 2H, $COCH_2$), 5.53 (s, 2H, OCH_2), 7.14–7.90 (m, 8H, Ar–H), 7.77 (s, 1H, CH), 9.12 (s, 1H, COOH). MS *m/z* 448 (M + 1). Anal. Calcd. for $C_{20}H_{14}ClNO_5S_2$: C, 53.63; H, 3.15; N, 3.13. Found: C, 53.41; H, 3.24; N, 3.22.

*5.5.2. (Z)-2-(5-(4-(2-(3-chlorophenyl)-2-oxoethoxy)benzylidene)-4-oxo-2-thioxothia-zolidin-3-yl)acetic acid (**II-b**)*

Yield 89%; m.p. 272–274 °C. IR (KBr) cm^{-1}: 3414 (OH), 1700 (C=O). ^1H NMR (DMSO-d_6, 300 MHz, ppm): δ 4.51 (s, 2H, $COCH_2$), 5.75 (s, 2H, OCH_2), 7.18–8.08 (m, 8H, Ar–H), 7.81 (s, 1H, CH), 9.21 (s, 1H, COOH). MS *m/z* 448 (M + 1). Anal. Calcd. for $C_{20}H_{14}ClNO_5S_2$: C, 53.63; H, 3.15; N, 3.13. Found: C, 53.79; H, 3.27; N, 3.19.

*5.5.3. (Z)-2-(5-(4-(2-(4-chlorophenyl)-2-oxoethoxy)benzylidene)-4-oxo-2-thioxothia-zolidin-3-yl)acetic acid (**II-c**)*

Yield 90%; m.p. 202–204 °C. IR (KBr) cm^{-1}: 3411 (OH), 1699 (C=O). ^1H NMR (DMSO-d_6, 300 MHz, ppm): δ 4.36 (s, 2H, $COCH_2$), 5.73 (s, 2H, OCH_2), 7.16–8.06 (m, 8H, Ar–H), 7.77 (s, 1H, CH), 9.31 (s, 1H, COOH). MS *m/z* 448 (M + 1). Anal. Calcd. for $C_{20}H_{14}ClNO_5S_2$: C, 53.63; H, 3.15; N, 3.13. Found: C, 53.87; H, 3.18; N, 3.27.

*5.5.4. (Z)-2-(5-(4-(2-(2,4-dichlorophenyl)-2-oxoethoxy) benzylidene)-4-oxo-2-thioxoth-iazolidin-3-yl)acetic acid (**II-d**)*

Yield 84%; m.p. 238–240 °C. IR (KBr) cm^{-1}: 3408 (OH), 1696 (C=O). ^1H NMR (DMSO-d_6, 300 MHz, ppm): δ 4.52 (s, 2H, $COCH_2$), 5.52 (s, 2H, OCH_2), 7.14–7.96 (m, 7H, Ar–H), 7.81 (s, 1H, CH), 9.52 (s,1H, COOH). MS *m/z* 482 (M + 1). Anal. Calcd. for $C_{20}H_{13}Cl_2NO_5S_2$: C, 49.80; H, 2.72; N, 2.90. Found: C, 49.97; H, 2.90; N, 2.75.

*5.5.5. (Z)-2-(5-(4-(2-(2-bromophenyl)-2-oxoethoxy)benzylidene)-4-oxo-2-thioxothia-zolidin-3-yl)acetic acid (**II-e**)*

Yield 87%; m.p. 186–188 °C. IR (KBr) cm^{-1}: 3398 (OH), 1703 (C=O). ^1H NMR (DMSO-d_6, 300 MHz, ppm): δ 4.35 (s, 2H, $COCH_2$), 5.50 (s, 2H, OCH_2), 7.16–7.87 (m, 8H, Ar–H), 7.77 (s, 1H, CH), 9.14 (s, 1H, COOH). MS *m/z* 492 (M + 1). Anal. Calcd. for $C_{20}H_{14}BrNO_5S_2$: C, 48.79; H, 2.87; N, 2.84. Found: C, 48.66; H, 2.59; N, 3.01.

*5.5.6. (Z)-2-(5-(4-(2-(3-bromophenyl)-2-oxoethoxy)benzylidene)-4-oxo-2-thioxothia-zolidin-3-yl)acetic acid (**II-f**)*

Yield 86%; m.p. 254–256 °C. IR (KBr) cm^{-1}: 3396 (OH), 1707 (C=O). ^1H NMR (DMSO-d_6, 300 MHz, ppm): δ 4.33 (s, 2H, $COCH_2$), 5.75 (s, 2H, OCH_2), 7.18–8.20 (m, 8H, Ar–H), 7.76 (s, 1H, CH), 12.49 (s, 1H,

COOH). MS *m/z* 492 (M + 1). Anal. Calcd. for $C_{20}H_{14}BrNO_5S_2$: C, 48.79; H, 2.87; N, 2.84. Found: C, 48.84; H, 2.98; N, 2.88.

*5.5.7. (Z)-2-(5-(4-(2-(4-bromophenyl)-2-oxoethoxy)benzylidene)-4-oxo-2-thioxothia-zolidin-3-yl)acetic acid (**II-g**)*

Yield 83%; m.p. 259–261 °C IR (KBr) cm^{-1}: 3395 (OH), 1705 (C=O). ^1H NMR (DMSO-d_6, 300 MHz, ppm): δ 4.71 (s, 2H, COCH$_2$), 5.72 (s, 2H, OCH$_2$), 7.16–7.97 (m, 8H, Ar–H), 7.86 (s, 1H, CH), 13.5 (s, 1H, COOH). MS *m/z* 492 (M + 1). Anal. Calcd. for $C_{20}H_{14}BrNO_5S_2$: C, 48.79; H, 2.87; N, 2.84. Found: C, 48.91; H, 2.96; N, 2.88.

*5.5.8. (Z)-2-(5-(4-(2-(2-fluorophenyl)-2-oxoethoxy)benzylidene)-4-oxo-2-thioxothia-zolidin-3-yl)acetic acid (**II-h**)*

Yield 88%; m.p. 212–214 °C. IR (KBr) cm^{-1}: 3416 (OH), 1706 (C=O). ^1H NMR (DMSO-d_6, 300 MHz, ppm): δ 4.46 (s, 2H, COCH$_2$), 5.54 (s, 2H, OCH$_2$), 7.14–7.97 (m, 8H, Ar–H), 7.79 (s, 1H,CH), 9.07 (s, 1H, COOH). MS *m/z* 432 (M + 1). Anal. Calcd. for $C_{20}H_{14}FNO_5S_2$: C, 55.68; H, 3.27; N, 3.25. Found: C, 55.85; H, 3.34; N, 3.08.

*5.5.9. (Z)-2-(5-(4-(2-(4-fluorophenyl)-2-oxoethoxy)benzylidene)-4-oxo-2-thioxothia-zolidin-3-yl)acetic acid (**II-i**)*

Yield 87%; m.p. 208–210 °C. IR (KBr) cm^{-1}: 3418 (OH), 1707 (C=O). ^1H NMR (DMSO-d_6, 300 MHz, ppm): δ 4.35 (s, 2H, COCH$_2$), 5.73 (s, 2H, OCH$_2$), 7.16–8.15 (m, 8H, Ar–H), 7.77 (s, 1H, CH), 9.13 (s, 1H, COOH). MS *m/z* 432 (M + 1). Anal. Calcd. for $C_{20}H_{14}FNO_5S_2$: C, 55.68; H, 3.27; N, 3.25. Found: C, 55.57; H, 3.32; N, 3.41.

*5.5.10. (Z)-2-(4-oxo-5-(4-(2-oxo-2-phenylethoxy)benzylidene)-2-thioxothiazolidin-3-yl)acetic acid (**II-j**)*

Yield 85%; m.p. 252–254 °C. IR (KBr) cm^{-1}: 3397 (OH), 1695 (C=O). ^1H NMR (DMSO-d_6, 300 MHz, ppm): δ 4.36 (s, 2H, COCH$_2$), 5.74 (s, 2H, OCH$_2$), 7.15–8.05 (m, 9H, Ar–H), 7.76 (s, 1H, CH), 9.32 (s, 1H, COOH). MS *m/z* 414 (M + 1). Anal. Calcd. for $C_{20}H_{15}NO_5S_2$: C, 58.10; H, 3.66; N, 3.39. Found: C, 57.95; H, 3.78; N, 3.41.

*5.5.11. (Z)-2-(4-oxo-5-(4-(2-oxo-2-(p-tolyl)ethoxy)benzylidene)-2-thioxothiazolidin-3-yl)acetic acid (**II-k**)*

Yield 86%; m.p. 222–224 °C. IR (KBr) cm^{-1}: 3406 (OH), 1701 (C=O). ^1H NMR (DMSO-d_6, 300 MHz, ppm): δ 2.41 (s, 3H, CH$_3$), 4.43 (s, 2H, COCH$_2$), 5.69 (s, 2H, OCH$_2$), 7.14–7.95 (m, 8H, Ar–H), 7.78 (s, 1H, CH), 9.24 (s, 1H, COOH). MS *m/z* 428 (M + 1). Anal. Calcd. for $C_{21}H_{17}NO_5S_2$: C, 59.00; H, 4.01; N, 3.28. Found: C, 59.16; H, 4.10; N, 3.17.

*5.5.12. (Z)-2-(5-(4-(2-(3-methoxyphenyl)-2-oxoethoxy) benzylidene)-4-oxo-2-thioxoth-iazolidin-3-yl)acetic acid (**II-l**)*

Yield 91%; m.p. 258–260 °C. IR (KBr) cm^{-1}: 3403 (OH), 1709 (C=O). ^1H NMR (DMSO-d_6, 300 MHz, ppm): δ 3.84 (s, 3H, OCH$_3$), 4.34 (s, 2H, COCH$_2$), 5.73 (s, 2H, OCH$_2$), 7.15–7.77 (m, 8H, Ar–H), 7.77 (s, 1H, CH), 9.05 (s, 1H, COOH). MS *m/z* 444 (M + 1). Anal. Calcd. for $C_{21}H_{17}NO_6S_2$: C, 56.87; H, 3.86; N, 3.16. Found: C, 56.74; H, 3.93; N, 3.29.

*5.5.13. (Z)-2-(5-(4-(2-(4-methoxyphenyl)-2-oxoethoxy) benzylidene)-4-oxo-2-thioxoth-iazolidin-3-yl)acetic acid (**II-m**)*

Yield 89%; m.p. 260–262 °C. IR (KBr) cm^{-1}: 3404 (OH), 1708 (C=O). ^1H NMR (DMSO-d_6, 300 MHz, ppm): δ 3.87 (s, 3H, OCH$_3$), 4.46 (s, 2H, COCH$_2$), 5.66 (s, 2H, OCH$_2$), 7.09–8.03 (m, 8H, Ar–H), 7.79 (s, 1H, CH), 9.17 (s, 1H, COOH). MS *m/z* 444 (M + 1). Anal. Calcd. for $C_{21}H_{17}NO_6S_2$: C, 56.87; H, 3.86; N, 3.16. Found: C, 56.99; H, 3.69; N, 3.04.

*5.6. General procedure for the preparation of compounds **III***

A mixture of **3** (3 mmol), (S)-2-(4-oxo-2-thioxothiazolidin-3-yl)-3-phenylpropanoic acid (3 mmol), 10 drops glacial acetic acid and 10 drops piperidine in ethanol (20 mL) was refluxed for 4 h. After cooling, the solvent was evaporated *in vacuo*, followed by the purification of the resulting residue by silica gel column chromatography (dichloromethane/methanol/acetic acid, 100:1:0.5) to obtain a yellow solid.

*5.6.1. (S,Z)-2-(5-(4-(2-(2-chlorophenyl)-2-oxoethoxy)benzylidene)-4-oxo-2-thioxothia-zolidin-3-yl)-3-phenylpropanoic acid (**III-a**)*

Yield 70%; m.p. 84–85 °C. IR (KBr) cm^{-1}: 3422 (OH), 1693 (C=O). ^1H NMR (DMSO-d_6, 300 MHz, ppm): δ 3.49 (d, 2H, *J* = 6.1 Hz, CHCH$_2$), 5.71 (s, 2H, COCH$_2$), 5.86 (br.s, 1H, CH$_2$CH), 7.75 (s, 1H, ph-CH), 7.13-8.04 (m, 13H, Ar–H), 13.45 (s, 1H, COOH). MS *m/z* 538 (M + 1). Anal. Calcd. for $C_{27}H_{20}ClNO_5S_2$: C, 60.27; H, 3.75; N, 2.60. Found: C, 60.41; H, 3.84; N, 2.72.

*5.6.2. (S,Z)-2-(5-(4-(2-(3-chlorophenyl)-2-oxoethoxy)benzylidene)-4-oxo-2-thioxothia-zolidin-3-yl)-3-phenylpropanoic acid (**III-b**)*

Yield 71%; m.p. 74–75 °C. IR (KBr) cm^{-1}: 3423 (OH), 1696 (C=O). ^1H NMR (DMSO-d_6, 300 MHz, ppm): δ 3.50 (d, 2H, *J* = 5.9 Hz, CHCH$_2$), 5.74 (s, 2H, COCH$_2$), 5.87 (br.s, 1H, CH$_2$CH), 7.76 (s, 1H, ph-CH), 7.15–8.06 (m, 13H, Ar–H), 13.37 (s, 1H, COOH). MS *m/z* 538 (M + 1). Anal. Calcd. for $C_{27}H_{20}ClNO_5S_2$: C, 60.27; H, 3.75; N, 2.60. Found: C, 60.52; H, 3.85; N, 2.39.

*5.6.3. (S,Z)-2-(5-(4-(2-(4-chlorophenyl)-2-oxoethoxy)benzylidene)-4-oxo-2-thioxothia-zolidin-3-yl)-3-phenylpropanoic acid (**III-c**)*

Yield 65%; m.p. 65–67 °C. IR (KBr) cm^{-1}: 3420 (OH), 1691 (C=O). ^1H NMR (DMSO-d_6, 300 MHz, ppm): δ 3.49 (d, 2H, *J* = 5.7 Hz, CHCH$_2$), 5.51 (s, 2H, COCH$_2$), 5.87 (br.s, 1H, CH$_2$CH), 7.75 (s, 1H, ph-CH), 7.12–7.88 (m, 13H, Ar–H), 13.42 (s, 1H, COOH). MS *m/z* 538 (M + 1). Anal. Calcd. for $C_{27}H_{20}ClNO_5S_2$: C, 60.27; H, 3.75; N, 2.60. Found: C, 60.54; H, 3.86; N, 2.60.

*5.6.4. (S,Z)-2-(5-(4-(2-(2,4-dichlorophenyl)-2-oxoethoxy) benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl)-3-phenylpropanoic acid (**III-d**)*

Yield 68%; m.p.84–85 °C. IR (KBr) cm^{-1}: 3435 (OH), 1708 (C=O). ^1H NMR (DMSO-d_6, 300 MHz, ppm): δ 3.49 (d, 2H, *J* = 6.4 Hz, CHCH$_2$), 5.73 (s, 2H, COCH$_2$), 5.86 (br.s, 1H, CH$_2$CH), 7.75 (s, 1H, ph-CH), 7.07–7.72 (m, 12H, Ar–H), 13.48 (s, 1H, COOH). MS *m/z* 572 (M + 1). Anal. Calcd. for $C_{27}H_{19}Cl_2NO_5S_2$: C, 56.65; H, 3.35; N, 2.45. Found: C, 56.78; H, 3.16; N, 2.54.

*5.6.5. (S,Z)-2-(5-(4-(2-(2-bromophenyl)-2-oxoethoxy)benzylidene)-4-oxo-2-thioxothia-zolidin-3-yl)-3-phenylpropanoic acid (**III-e**)*

Yield 71%; m.p. 77–78 °C. IR (KBr) cm^{-1}: 3432 (OH), 1708 (C=O). ^1H NMR (DMSO-d_6, 300 MHz, ppm): δ 3.49 (d, 2H, *J* = 7.1 Hz, CHCH$_2$), 5.50 (s, 2H, COCH$_2$), 5,86 (br.s, 1H, CH$_2$CH), 7.75 (s, 1H, ph-CH), 7.13–7.84 (m, 13H, Ar–H), 13.45 (s, 1H, COOH). MS *m/z* 582 (M + 1). Anal. Calcd. for $C_{27}H_{20}BrNO_5S_2$: C, 55.67; H, 3.46; N, 2.40. Found: C, 55.73; H, 3.53; N, 2.53.

*5.6.6. (S,Z)-2-(5-(4-(2-(3-bromophenyl)-2-oxoethoxy)benzylidene)-4-oxo-2-thioxothia-zolidin-3-yl)-3-phenylpropanoic acid (**III-f**)*

Yield 70%; m.p. 90–91 °C. IR (KBr) cm^{-1}: 3431 (OH), 1703 (C=O). ^1H NMR (DMSO-d_6, 300 MHz, ppm): δ 3.49 (d, 2H, *J* = 7.4 Hz, CHCH$_2$), 5.73 (s, 2H, COCH$_2$), 5.87 (br.s, 1H, CH$_2$CH), 7.75 (s, 1H, ph-CH), 7.15–8.17 (m, 13H, Ar–H), 13.44 (s, 1H, COOH). MS *m/z* 582 (M + 1). Anal. Calcd. for $C_{27}H_{20}BrNO_5S_2$: C, 55.67; H, 3.46; N, 2.40. Found: C, 55.43; H, 3.51; N, 2.32.

*5.6.7. (S,Z)-2-(5-(4-(2-(4-bromophenyl)-2-oxoethoxy)benzylidene)-4-oxo-2-thioxothia-zolidin-3-yl)-3-phenylpropanoic acid (**III-g**)*

Yield 63%; m.p. 92–93 °C. IR (KBr) cm^{-1}: 3435 (OH), 1705 (C=O). ^1H NMR (DMSO-d_6, 300 MHz, ppm): δ 3.49 (d, 2H, *J* = 7.0 Hz,

CHCH$_2$), 5.71 (s, 2H, COCH$_2$), 5.86 (br.s, 1H, CH$_2$CH), 7.75 (s, 1H, ph-CH), 7.13–7.96 (m, 13H, Ar–H), 13.43 (s, 1H, COOH). MS *m/z* 582 (M + 1). Anal. Calcd. for $C_{27}H_{20}BrNO_5S_2$: C, 55.67; H, 3.46; N, 2.40. Found: C, 55.52; H, 3.61; N, 2.30.

*5.6.8. (S,Z)-2-(5-(4-(2-(2-fluorophenyl)-2-oxoethoxy)benzylidene)-4-oxo-2-thioxothia-zolidin-3-yl)-3-phenylpropanoic acid (**III-h**)*

Yield 62%; m.p. 80–81 °C. IR (KBr) cm^{-1}: 3419 (OH), 1700 (C=O). ^{1}H NMR (DMSO-d_6, 300 MHz, ppm): δ 3.49 (d, 2H, J = 6.4 Hz, CHCH$_2$), 5.53 (s, 2H, COCH$_2$), 5.86 (br.s, 1H, CH$_2$CH), 7.75 (s, 1H, ph-CH), 7.12–7.95 (m, 13H, Ar–H), 13.42 (s, 1H, COOH). MS *m/z* 522 (M + 1). Anal. Calcd. for $C_{27}H_{20}FNO_5S_2$: 62.17; H, 3.86; N, 2.69. Found: C, 62.04; H, 3.98; N, 2.83.

*5.6.9. (S,Z)-2-(5-(4-(2-(4-fluorophenyl)-2-oxoethoxy)benzylidene)-4-oxo-2-thioxothia-zolidin-3-yl)-3-phenylpropanoic acid (**III-I**)*

Yield 64%; m.p. 78–80 °C. IR (KBr) cm^{-1}: 3421 (OH), 1702 (C=O). ^{1}H NMR (DMSO-d_6, 300 MHz, ppm): δ 3.49 (d, 2H, J = 7.2 Hz, CHCH$_2$), 5.72 (s, 2H, COCH$_2$), 5.87 (br.s, 1H, CH$_2$CH), 7.75 (s, 1H, ph-CH), 7.13–8.13 (m, 13H, Ar–H), 13.44 (s, 1H, COOH). MS *m/z* 522 (M + 1). Anal. Calcd. for $C_{27}H_{20}FNO_5S_2$: C, 62.17; H, 3.86; N, 2.69. Found: C, 62.02; H, 3.99; N, 2.71.

*5.6.10. (S,Z)-2-(4-oxo-5-(4-(2-oxo-2-phenylethoxy)benzylidene)-2-thioxothiazolidin-3-yl)-3-phenylpropanoic acid (**III-J**)*

Yield 65%; m.p. 88–89 °C. IR (KBr) cm^{-1}: 3415 (OH), 1701 (C=O). ^{1}H NMR (DMSO-d_6, 300 MHz, ppm): δ 3.61 (d, 2H, J = 7.3 Hz, CHCH$_2$), 5.74 (s, 2H, COCH$_2$), 5.88 (br.s, 1H, CH$_2$CH), 7.77 (s, 1H, ph-CH), 7.14–8.04 (m, 14H, Ar–H), 13.39 (s, 1H, COOH). MS *m/z* 504 (M + 1). Anal. Calcd. for $C_{27}H_{21}NO_5S_2$: Found: C, 64.40; H, 4.20; N, 2.78. Found: C, 64.31; H, 4.24; N, 2.84.

*5.6.11. (S,Z)-2-(4-oxo-5-(4-(2-oxo-2-(p-tolyl)ethoxy)benzylidene)-2-thioxothiazolidin-3-yl)-3-phenylpropanoic acid (**III-k**)*

Yield 69%; m.p. 98–99 °C. IR (KBr) cm^{-1}: 3424 (OH), 1708 (C=O). ^{1}H NMR (DMSO-d_6, 300 MHz, ppm): δ 2.39 (s, 3H, CH$_3$), 3.49 (d, 2H, J = 6.8 Hz, CHCH$_2$), 5.68 (s, 2H, COCH$_2$), 5.87 (br.s, 1H, CH$_2$CH), 7.75 (s, 1H, ph-CH), 7.11–7.93 (m, 13H, Ar–H), 13.45 (s, 1H, COOH). MS *m/z* 518 (M + 1). Anal. Calcd. for $C_{28}H_{23}NO_5S_2$: C, 64.97; H, 4.48; N, 2.71. Found: C, 65.13; H, 4.53; N, 2.84.

*5.6.12. (S,Z)-2-(5-(4-(2-(3-methoxyphenyl)-2-oxoethoxy) benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl)-3-phenylpropanoic acid (**III-l**)*

Yield 71%; m.p. 82–83 °C. IR (KBr) cm^{-1}: 3428 (OH), 1713 (C=O). ^{1}H NMR (DMSO-d_6, 300 MHz, ppm): δ 3.49 (d, 2H, J = 7.4 Hz, CHCH$_2$), 3.83 (s, 3H, OCH$_3$), 5.72 (s, 2H, COCH$_2$), 5.87 (br.s, 1H, CH$_2$CH), 7.75 (s, 1H, ph-CH), 7.12–7.75 (m, 13H, Ar–H), 13.42 (s, 1H, COOH). MS *m/z* 534 (M + 1). Anal. Calcd. for $C_{28}H_{23}NO_6S_2$: C, 63.02; H, 4.34; N, 2.62. Found: C, 62.87; H, 4.44; N, 2.49.

*5.6.13. (S,Z)-2-(5-(4-(2-(4-methoxyphenyl)-2-oxoethoxy) benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl)-3-phenylpropanoic acid (**III-m**)*

Yield 65%; m.p. 85–87 °C. IR (KBr) cm^{-1}: 3421 (OH), 1711 (C=O). ^{1}H NMR (DMSO-d_6, 300 MHz, ppm): δ 3.49 (d, 2H, J = 6.9 Hz, CHCH$_2$), 3.85 (s, 3H, OCH$_3$), 5.65 (s, 2H, COCH$_2$), 5.86 (br.s, 1H, CH$_2$CH), 7.75 (s, 1H, ph-CH), 7.07–8.01 (m, 13H, Ar–H), 13.43 (s, 1H, COOH). MS *m/z* 534 (M + 1). Anal. Calcd. for $C_{28}H_{23}NO_6S_2$: C, 63.02; H, 4.34; N, 2.62. Found: C, 63.24; H, 4.47; N, 2.53.

*5.7. General procedure for the preparation of compounds **IV***

A mixture of **3** (3 mmol), (S)-3-(4-hydroxyphenyl)-2-(4-oxo-2-thioxothiazolidin-3-yl)propanoic acid (3 mmol), 10 drops glacial acetic acid and 10 drops piperidine in ethanol (20 mL) was refluxed for 4 h. After cooling, the solvent was evaporated *in vacuo*, followed by the purification of the resulting residue by silica gel column chromatography (dichloromethane/methanol/acetic acid, 100:1:1) to obtain a yellow solid.

*5.7.1. (S,Z)-2-(5-(4-(2-(2-chlorophenyl)-2-oxoethoxy)benzylidene)-4-oxo-2-thioxothia-zolidin-3-yl)-3-(4-hydroxyphenyl)propanoic acid (**IV-a**)*

Yield 56%; m.p. 178–180 °C. IR (KBr) cm^{-1}: 3394 3177 (OH), 1697 (C=O). ^{1}H NMR (DMSO-d_6, 300 MHz, ppm): δ 3.55 (s, 2H, CHCH$_2$), 5.52 (s, 2H, COCH$_2$), 5.77 (s, 1H, CH$_2$CH), 7.76 (s, 1H, ph-CH), 6.54–7.86 (m, 12H, Ar–H), 9.20 (s, 1H, OH), 13.30 (s, 1H, COOH). MS *m/z* 554 (M + 1). Anal. Calcd. for $C_{27}H_{20}ClNO_6S_2$: C, 58.53; H, 3.64; N, 2.53. Found: C, 58.41; H, 3.52; N, 2.68.

*5.7.2. (S,Z)-2-(5-(4-(2-(3-chlorophenyl)-2-oxoethoxy) benzylidene)-4-oxo-2-thioxothia-zolidin-3-yl)-3-(4-hydroxyphenyl)propanoic acid (**IV-b**)*

Yield 57%; m.p. 246–248 °C. IR (KBr) cm^{-1}: 3396 3175 (OH), 1694 (C=O). ^{1}H NMR (DMSO-d_6, 300 MHz, ppm): δ 3.55 (s, 2H, CHCH$_2$), 5.55 (s, 2H, COCH$_2$), 5.79 (s, 1H, CH$_2$CH), 7.76 (s, 1H, ph-CH), 6.54–8.06 (m, 12H, Ar–H), 9.20 (s, 1H, OH), 13.40 (s, 1H, COOH). MS *m/z* 554 (M + 1). Anal. Calcd. for $C_{27}H_{20}ClNO_6S_2$: C, 58.53; H, 3.64; N, 2.53. Found: C, 58.40; H, 3.76; N, 2.65.

*5.7.3. (S,Z)-2-(5-(4-(2-(4-chlorophenyl)-2-oxoethoxy)benzylidene)-4-oxo-2-thioxothia-zolidin-3-yl)-3-(4-hydroxyphenyl)propanoic acid (**IV-c**)*

Yield 60%; m.p. 241–242 °C. IR (KBr) cm^{-1}: 3397 3176 (OH), 1695 (C=O). ^{1}H NMR (DMSO-d_6, 300 MHz, ppm): δ 3.55 (s, 2H, CHCH$_2$), 5.52 (s, 2H, COCH$_2$), 5.75 (s, 1H, CH$_2$CH), 7.76 (s, 1H, ph-CH), 6.54–8.04 (m, 12H, Ar–H), 9.20 (s, 1H, OH), 13.39 (s, 1H, COOH). MS *m/z* 554 (M + 1). Anal. Calcd. for $C_{27}H_{20}ClNO_6S_2$: C, 58.53; H, 3.64; N, 2.53. Found: C, 58.71; H, 3.56; N, 2.44.

*5.7.4. (S,Z)-2-(5-(4-(2-(2,4-dichlorophenyl)-2-oxoethoxy) benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl)-3-(4-hydroxyphenyl) propanoic acid (**IV-d**)*

Yield 53%; m.p.188–189 °C. IR (KBr) cm^{-1}: 3391 3172 (OH), 1693 (C=O). ^{1}H NMR (DMSO-d_6, 300 MHz, ppm): δ 3.55 (s, 2H, CHCH$_2$), 5.52 (s, 2H, COCH$_2$), 5.77 (s, 1H, CH$_2$CH), 7.76 (s, 1H, ph-CH), 6.54–7.91 (m, 11H, Ar–H), 9.20 (s, 1H, OH), 13.29 (s, 1H, COOH). MS *m/z* 588 (M + 1). Anal. Calcd. for $C_{27}H_{19}Cl_2NO_6S_2$: C, 55.11; H, 3.25; N, 2.38. Found: C, 54.89; H, 3.14; N, 2.47.

*5.7.5. (S,Z)-2-(5-(4-(2-(2-bromophenyl)-2-oxoethoxy) benzylidene)-4-oxo-2-thioxothia-zolidin-3-yl)-3-(4-hydroxyphenyl) propanoic acid (**IV-e**)*

Yield 57%; m.p. 165–166 °C. IR (KBr) cm^{-1}: 3398 3182 (OH), 1702 (C=O). ^{1}H NMR (DMSO-d_6, 300 MHz, ppm): δ 3.55 (s, 2H, CHCH$_2$), 5.50 (s, 2H, COCH$_2$), 5.78 (s, 1H, CH$_2$CH), 7.75 (s, 1H, ph-CH), 6.54–7.77 (m, 12H, Ar–H), 9.19 (s, 1H, OH), 13.38 (s, 1H, COOH). MS *m/z* 598 (M + 1). Anal. Calcd. for $C_{27}H_{20}BrNO_6S_2$: C, 54.18; H, 3.37; N, 2.34. Found: C, 54.04; H, 3.42; N, 2.46.

*5.7.6. (S,Z)-2-(5-(4-(2-(3-bromophenyl)-2-oxoethoxy) benzylidene)-4-oxo-2-thioxothia-zolidin-3-yl)-3-(4-hydroxyphenyl) propanoic acid (**IV-f**)*

Yield 51%; m.p. 238–239 °C. IR (KBr) cm^{-1}: 3398 3183 (OH), 1704 (C=O). ^{1}H NMR (DMSO-d_6, 300 MHz, ppm): δ 3.55 (s, 2H, CHCH$_2$), 5.54 (s, 2H, COCH$_2$), 5.79 (s, 1H, CH$_2$CH), 7.76 (s, 1H, ph-CH), 6.54–8.18 (m, 12H, Ar–H), 9.20 (s, 1H, OH), 13.34 (s, 1H, COOH). MS *m/z* 598 (M + 1). Anal. Calcd. for $C_{27}H_{20}BrNO_6S_2$: C, 54.18; H, 3.37; N, 2.34. Found: C, 54.36; H, 3.24; N, 2.45.

*5.7.7. (S,Z)-2-(5-(4-(2-(4-bromophenyl)-2-oxoethoxy)benzylidene)-4-oxo-2-thioxothia-zolidin-3-yl)-3-(4-hydroxyphenyl)propanoic acid (**IV-g**)*

Yield 55%; m.p. 247–249 °C. IR (KBr) cm^{-1}: 3399 3184 (OH), 1704 (C=O). ^1H NMR (DMSO-d_6, 300 MHz, ppm): δ 3.55 (s, 2H, CHC$\underline{H}_2$), 5.55 (s, 2H, COC$\underline{H}_2$), 5.75 (s, 1H, CH$_2$C$\underline{H}$), 7.79 (s, 1H, ph-C$\underline{H}$), 6.54–7.93 (m, 12H, Ar–$\underline{H}$), 9.20 (s, 1H, O$\underline{H}$), 13.40 (s, 1H, COO$\underline{H}$). MS *m/z* 598 (M + 1). Anal. Calcd. for $C_{27}H_{20}BrNO_6S_2$: C, 54.18; H, 3.37; N, 2.34. Found: C, 54.96; H, 3.27; N, 2.22.

*5.7.8. (S,Z)-2-(5-(4-(2-(2-fluorophenyl)-2-oxoethoxy)benzylidene)-4-oxo-2-thioxothia-zolidin-3-yl)-3-(4-hydroxyphenyl)propanoic acid (**IV-h**)*

Yield 54%; m.p. 219–220 °C. IR (KBr) cm^{-1}: 3389 3173 (OH), 1695 (C=O). ^1H NMR (DMSO-d_6, 300 MHz, ppm): δ 3.55 (s, 2H, CHC$\underline{H}_2$), 5.53 (s, 2H, COC$\underline{H}_2$), 5.75 (s, 1H, CH$_2$C$\underline{H}$), 7.75 (s, 1H, ph-C$\underline{H}$), 6.54–7.75 (m, 12H, Ar–$\underline{H}$), 9.20 (s, 1H, O$\underline{H}$), 13.40 (s, 1H, COO$\underline{H}$). MS *m/z* 538 (M + 1). Anal. Calcd. for $C_{27}H_{20}FNO_6S_2$: C, 60.32; H, 3.75; N, 2.61. Found: C, 60.15; H, 3.71; N, 2.76.

*5.7.9. (S,Z)-2-(5-(4-(2-(4-fluorophenyl)-2-oxoethoxy)benzylidene)-4-oxo-2-thioxothia-zolidin-3-yl)-3-(4-hydroxyphenyl)propanoic acid (**IV-i**)*

Yield 57%; m.p. 237–238 °C. IR (KBr) cm^{-1}: 3386 3171 (OH), 1694 (C=O). ^1H NMR (DMSO-d_6, 300 MHz, ppm): δ 3.56 (s, 2H, CHC$\underline{H}_2$), 5.52 (s, 2H, COC$\underline{H}_2$), 5.79 (s, 1H, CH$_2$C$\underline{H}$), 7.76 (s, 1H, ph-C$\underline{H}$), 6.54–8.10 (m, 12H, Ar–$\underline{H}$), 9.20 (s, 1H, O$\underline{H}$), 13.35 (s, 1H, COO$\underline{H}$). MS *m/z* 538 (M + 1). Anal. Calcd. for $C_{27}H_{20}FNO_6S_2$: C, 60.32; H, 3.75; N, 2.61. Found: C, 60.17; H, 3.87; N, 2.47.

*5.7.10. (S,Z)-3-(4-hydroxyphenyl)-2-(4-oxo-5-(4-(2-oxo-2-phenylethoxy)benzylidene)-2-thioxothiazolidin-3-yl)propanoic acid (**IV-j**)*

Yield 59%; m.p.229–230 °C. IR (KBr) cm^{-1}: 3391 3171 (OH), 1692 (C=O). ^1H NMR (DMSO-d_6, 300 MHz, ppm): δ 3.55 (s, 2H, CHC$\underline{H}_2$), 5.52 (s, 2H, COC$\underline{H}_2$), 5.74 (s, 1H, CH$_2$C$\underline{H}$), 7.76 (s, 1H, ph-C$\underline{H}$), 6.54–7.86 (m, 12H, Ar–$\underline{H}$), 9.20 (s, 1H, O$\underline{H}$), 13.39 (s, 1H, COO$\underline{H}$). MS *m/z* 520(M + 1). Anal. Calcd. for $C_{27}H_{21}NO_6S_2$: C, 62.41; H, 4.07; N, 2.70. Found: C, 62.68; H, 4.23; N, 2.69.

*5.7.11. (S,Z)-3-(4-hydroxyphenyl)-2-(4-oxo-5-(4-(2-oxo-2-(p-tolyl) ethoxy)benzylide-ne)-2-thioxothiazolidin-3-yl)propanoic acid (**IV-k**)*

Yield 54%; m.p. 240–242 °C. IR (KBr) cm^{-1}: 3393 3174 (OH), 1682 (C=O). ^1H NMR (DMSO-d_6, 300 MHz, ppm): δ 2.51 (s, 3H, C$\underline{H}_3$), 3.55 (s, 2H, CHC$\underline{H}_2$), 5.70 (s, 2H, COC$\underline{H}_2$), 5.79 (s, 1H, CH$_2$C$\underline{H}$), 7.76 (s, 1H, ph-C$\underline{H}$), 6.56–7.94 (m, 12H, Ar–$\underline{H}$), 9.19 (s, 1H, O$\underline{H}$), 13.36 (s, 1H, COO$\underline{H}$). MS *m/z* 534 (M + 1). Anal. Calcd. for $C_{28}H_{23}NO_6S_2$: C, 63.02; H, 4.34; N, 2.62. Found: C, 62.87; H, 4.42; N, 2.78.

*5.7.12. (S,Z)-3-(4-hydroxyphenyl)-2-(5-(4-(2-(3-methoxyphenyl)-2-oxoethoxy)benzylid-ene)-4-oxo-2-thioxothiazolidin-3-yl) propanoic acid (**IV-l**)*

Yield 52%; m.p. 201–202 °C. IR (KBr) cm^{-1}: 3396 3177 (OH), 1685 (C=O). ^1H NMR (DMSO-d_6, 300 MHz, ppm): δ 3.56 (s, 2H, CHC$\underline{H}_2$), 3.83 (s, 3H, OCH$_3$) 5.53 (s, 2H, COC$\underline{H}_2$), 5.79 (s, 1H, CH$_2$C$\underline{H}$), 7.76 (s, 1H, ph-C$\underline{H}$), 6.54–7.76 (m, 12H, Ar–$\underline{H}$), 9.20 (s, 1H, O$\underline{H}$), 13.38 (s, 1H, COO$\underline{H}$). MS *m/z* 550 (M + 1). Anal. Calcd. for $C_{28}H_{23}NO_7S_2$: C, 61.19; H, 4.22; N, 2.55. Found: C, 61.02; H, 4.41; N, 2.34.

*5.7.13. (S,Z)-3-(4-hydroxyphenyl)-2-(5-(4-(2-(4-methoxyphenyl)-2-oxoethoxy)benzyli-dene)-4-oxo-2-thioxothiazolidin-3-yl) propanoic acid (**IV-m**)*

Yield 57%; m.p. 200–202 °C. IR (KBr) cm^{-1}: 3395 3178 (OH), 1687 (C=O). ^1H NMR (DMSO-d_6, 300 MHz, ppm): δ 3.52 (s, 2H, CHC$\underline{H}_2$), 3.55 (s, 3H, OC$\underline{H}_3$), 5.65 (s, 2H, COC$\underline{H}_2$), 5.77 (s, 1H, CH$_2$C$\underline{H}$), 7.74 (s, 1H, ph-C$\underline{H}$), 6.54–8.01 (m, 12H, Ar–$\underline{H}$), 9.17 (s, 1H, O$\underline{H}$), 13.27 (s, 1H, COO$\underline{H}$). MS *m/z* 550 (M + 1). Anal. Calcd. for $C_{28}H_{23}NO_7S_2$: C, 61.19; H, 4.22; N, 2.55. Found: C, 61.34; H, 4.28; N, 2.43.

*5.8. General procedure for the preparation of compounds **V***

A mixture of **3** (3 mmol), (S)-3-(1H-indol-3-yl)-2-(4-oxo-2-thioxothiazolidin-3-yl)propanoic acid (3 mmol), 10 drops glacial acetic acid and 10 drops piperidine in ethanol (20 mL) was refluxed for 4 h. After cooling, the solvent was evaporated *in vacuo*, followed by the purification of the resulting residue by silica gel column chromatography (dichloromethane/methanol/acetic acid, 80:1:1) to obtain a yellow solid.

*5.8.1. (S,Z)-2-(5-(4-(2-(2-chlorophenyl)-2-oxoethoxy)benzylidene)-4-oxo-2-thioxothia-zolidin-3-yl)-3-(1H-indol-3-yl)propanoic acid (**V-a**)*

Yield 50%; m.p. 205–206 °C. IR (KBr) cm^{-1}: 3433 (OH), 3042 (NH), 1692 (C=O). ^1H NMR (DMSO-d_6, 300 MHz, ppm): δ 3.58–3.76 (m, 2H, CHC$\underline{H}_2$), 5.50 (s, 2H, COC$\underline{H}_2$), 5.69 (br.s, 1H, CH$_2$C$\underline{H}$), 7.68 (s, 1H, ph-C$\underline{H}$), 6.88–8.12 (m, 13H, Ar–$\underline{H}$), 10.75 (s, 1H, N$\underline{H}$), 13.81 (s, 1H, COO$\underline{H}$). MS *m/z* 577 (M + 1). Anal. Calcd. for $C_{29}H_{21}ClN_2O_5S_2$: C, 60.36; H, 3.67; N, 4.85. Found: C, 60.21; H, 3.75; N, 4.97.

*5.8.2. (S,Z)-2-(5-(4-(2-(3-chlorophenyl)-2-oxoethoxy) benzylidene)-4-oxo-2-thioxothia-zolidin-3-yl)-3-(1H-indol-3-yl) propanoic acid (**V-b**)*

Yield 52%; m.p. 157–158 °C. IR (KBr) cm^{-1}: 3431 (OH), 3044 (NH), 1695 (C=O). ^1H NMR (DMSO-d_6, 300 MHz, ppm): δ 3.62–3.74 (m, 2H, CHC$\underline{H}_2$), 5.66 (br.s, 1H, CH$_2$C$\underline{H}$), 5.76 (s, 2H, COC$\underline{H}_2$), 7.64 (s, 1H, ph-C$\underline{H}$), 6.88–8.06 (m, 13H, Ar–$\underline{H}$), 10.76 (s, 1H, N$\underline{H}$), 13.61 (s, 1H, COO$\underline{H}$). MS *m/z* 577 (M + 1). Anal. Calcd. for $C_{29}H_{21}ClN_2O_5S_2$: C, 60.36; H, 3.67; N, 4.85. Found: C, 60.24; H, 3.61; N, 4.73.

*5.8.3. (S,Z)-2-(5-(4-(2-(4-chlorophenyl)-2-oxoethoxy) benzylidene)-4-oxo-2-thioxothia-zolidin-3-yl)-3-(1H-indol-3-yl) propanoic acid (**V-c**)*

Yield 57%; m.p. 234–236 °C. IR (KBr) cm^{-1}: 3432 (OH), 3043 (NH), 1694 (C=O). ^1H NMR (DMSO-d_6, 300 MHz, ppm): δ 3.58–3.77 (m, 2H, CHC$\underline{H}_2$), 5.63 (br.s, 1H, CH$_2$C$\underline{H}$), 5.70 (s, 2H, COC$\underline{H}_2$), 7.67 (s, 1H, ph-C$\underline{H}$), 6.88–8.04 (m, 13H, Ar–$\underline{H}$), 10.70 (s, 1H, N$\underline{H}$), 12.51 (s, 1H, COO$\underline{H}$). MS *m/z* 577 (M + 1). Anal. Calcd. for $C_{29}H_{21}ClN_2O_5S_2$: C, 60.36; H, 3.67; N, 4.85. Found: C, 60.15; H, 3.78; N, 4.91.

*5.8.4. (S,Z)-2-(5-(4-(2-(2,4-dichlorophenyl)-2-oxoethoxy) benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl)-3-(1H-indol-3-yl) propanoic acid (**V-d**)*

Yield59%; m.p. 117–119 °C. IR (KBr) cm^{-1}: 3425 (OH), 3037 (NH), 1697 (C=O). ^1H NMR (DMSO-d_6, 300 MHz, ppm): δ 3.57-3.73 (m, 2H, CHC$\underline{H}_2$), 5.51 (s, 2H, COC$\underline{H}_2$), 5.76 (br.s, 1H, CH$_2$C$\underline{H}$), 7.70 (s, 1H, ph-C$\underline{H}$), 6.96-7.94 (m, 12H, Ar–$\underline{H}$), 10.77 (s, 1H, N$\underline{H}$), 13.51 (s, 1H, COO$\underline{H}$). MS *m/z* 611 (M+1). Anal. Calcd. for $C_{29}H_{20}Cl_2N_2O_5S_2$: C, 56.96; H, 3.30; N, 4.58. Found: C, 57.13; H, 3.17; N, 4.67.

*5.8.5. (S,Z)-2-(5-(4-(2-(2-bromophenyl)-2-oxoethoxy) benzylidene)-4-oxo-2-thioxothia-zolidin-3-yl)-3-(1H-indol-3-yl) propanoic acid (**V-e**)*

Yield 53%; m.p. 156–158 °C. IR (KBr) cm^{-1}: 3421 (OH), 3067 (NH), 1699 (C=O). ^1H NMR (DMSO-d_6, 300 MHz, ppm): δ 3.57-3.76 (m, 2H, CHC$\underline{H}_2$), 5.48 (s, 2H, COC$\underline{H}_2$), 5.67 (br.s, 1H, CH$_2$C$\underline{H}$), 7.68 (s, 1H, ph-C$\underline{H}$), 6.86-7.84 (m, 13H, Ar–$\underline{H}$), 10.74 (s, 1H, N$\underline{H}$), 13.51 (s, 1H, COO$\underline{H}$). MS *m/z* 621 (M+1). Anal. Calcd. for $C_{29}H_{21}BrlN_2O_5S_2$: C, 56.04; H, 3.41; N, 4.51. Found: C, 56.25; H, 3.47; N, 4.37.

*5.8.6. (S,Z)-2-(5-(4-(2-(3-bromophenyl)-2-oxoethoxy) benzylidene)-4-oxo-2-thioxothia-zolidin-3-yl)-3-(1H-indol-3-yl) propanoic acid (**V-f**)*

Yield 57%; m.p. 115–116 °C. IR (KBr) cm^{-1}: 3424 (OH), 3063 (NH), 1698 (C=O). ^1H NMR (DMSO-d_6, 300 MHz, ppm): δ 3.57-3.74 (m, 2H, CHC$\underline{H}_2$), 5.73 (s, 2H, COC$\underline{H}_2$), 5.73 (br.s, 1H, $CH_2C\underline{H}$), 7.70 (s, 1H, ph-C$\underline{H}$), 6.88-8.18 (m, 13H, Ar–$\underline{H}$), 10.76 (s, 1H, N$\underline{H}$), 12.67 (s, 1H, COO$\underline{H}$). MS *m/z* 621 (M+1). Anal. Calcd. for $C_{29}H_{21}BrIN_2O_5S_2$: C, 56.04; H, 3.41; N, 4.51. Found: C, 55.96; H, 3.36; N, 4.46.

*5.8.7. (S,Z)-2-(5-(4-(2-(4-bromophenyl)-2-oxoethoxy) benzylidene)-4-oxo-2-thioxothia-zolidin-3-yl)-3-(1H-indol-3-yl) propanoic acid (**V-g**)*

Yield51%; m.p. 168–170 °C. IR (KBr) cm^{-1}: 3426 (OH), 3062 (NH), 1701 (C=O). ^1H NMR (DMSO-d_6, 300 MHz, ppm): δ 3.57–3.76 (m, 2H, CHC$\underline{H}_2$), 5.69 (br.s, 1H, $CH_2C\underline{H}$), 5.69 (s, 2H, COC$\underline{H}_2$), 7.67 (s, 1H, ph-C$\underline{H}$), 6.88-7.96 (m, 13H, Ar–$\underline{H}$), 10.72 (s, 1H, N$\underline{H}$), 12.57 (s, 1H, COO$\underline{H}$). MS *m/z* 621 (M+1). Anal. Calcd. for $C_{29}H_{21}BrIN_2O_5S_2$: C, 56.04; H, 3.41; N, 4.51. Found: C, 56.32; H, 3.54; N, 4.64.

*5.8.8. (S,Z)-2-(5-(4-(2-(2-fluorophenyl)-2-oxoethoxy)benzylidene)-4-oxo-2-thioxothia-zolidin-3-yl)-3-(1H-indol-3-yl)propanoic acid (**V-h**)*

Yield 53%; m.p. 219–220 °C. IR (KBr) cm^{-1}: 3428 (OH), 3047 (NH), 1696 (C=O). ^1H NMR (DMSO-d_6, 300 MHz, ppm): δ 3.58–3.76 (m, 2H, CHC$\underline{H}_2$), 5.52 (s, 2H, COC$\underline{H}_2$), 5.70 (br.s, 1H, $CH_2C\underline{H}$), 7.67 (s, 1H, ph-C$\underline{H}$), 6.96-7.67 (m, 13H, Ar–$\underline{H}$), 10.74 (s, 1H, N$\underline{H}$), 12.93 (s, 1H, COO$\underline{H}$). MS *m/z* 561 (M+1). Anal. Calcd. for $C_{29}H_{21}FIN_2O_5S_2$: C, 62.13; H, 3.78; N, 5.00. Found: C, 62.25; H, 3.93; N, 5.13.

*5.8.9. (S,Z)-2-(5-(4-(2-(4-fluorophenyl)-2-oxoethoxy)benzylidene)-4-oxo-2-thioxothia-zolidin-3-yl)-3-(1H-indol-3-yl)propanoic acid (**V-i**)*

Yield 58%; m.p. 188–189 °C. IR (KBr) cm^{-1}: 3429 (OH), 3042 (NH), 1697 (C=O). ^1H NMR (DMSO-d_6, 300 MHz, ppm): δ 3.58–3.77 (m, 2H, CHC$\underline{H}_2$), 5.63 (br.s, 1H, $CH_2C\underline{H}$), 5.70 (s, 2H, COC$\underline{H}_2$),, 7.67 (s, 1H, ph-C$\underline{H}$), 6.88–8.12 (m, 13H, Ar–$\underline{H}$), 10.73 (s, 1H, N$\underline{H}$), 12.51 (s, 1H, COO$\underline{H}$). MS *m/z* 561 (M + 1). Anal. Calcd. for $C_{29}H_{21}FN_2O_5S_2$: C, 62.13; H, 3.78; N, 5.00. Found: C, 61.97; H, 3.83; N, 4.88.

*5.8.10. (S,Z)-3-(1H-indol-3-yl)-2-(4-oxo-5-(4-(2-oxo-2-phenylethoxy) benzylidene)-2-thioxothiazolidin-3-yl)propanoic acid (**V-j**)*

Yield 54%; m.p. 227–228 °C. IR (KBr) cm^{-1}: 3417 (OH), 3056 (NH), 1692 (C=O). ^1H NMR (DMSO-d_6, 300 MHz, ppm): δ 3.57–3.73 (m, 2H, CHC$\underline{H}_2$), 5.72 (s, 2H, COC$\underline{H}_2$), 5.72 (br.s, 1H, $CH_2C\underline{H}$), 7.67 (s, 1H, ph-C$\underline{H}$), 6.89–8.03 (m, 14H, Ar–$\underline{H}$), 10.76 (s, 1H, N$\underline{H}$), 12.91 (s, 1H, COO$\underline{H}$). MS *m/z* 543 (M + 1). Anal. Calcd. for $C_{29}H_{22}N_2O_5S_2$: C, 64.19; H, 4.09; N, 5.16. Found: C, 64.05; H, 4.12; N, 5.31.

*5.8.11. (S,Z)-3-(1H-indol-3-yl)-2-(4-oxo-5-(4-(2-oxo-2-(p-tolyl) ethoxy)benzylidene)-2-thioxothiazolidin-3-yl)propanoic acid (**V-k**)*

Yield 57%; m.p. 230–232 °C. IR (KBr) cm^{-1}: 3428 (OH), 3044 (NH), 1694 (C=O). ^1H NMR (DMSO-d_6, 300 MHz, ppm): δ 2.39 (s, 3H, $C\underline{H}_3$), 3.58–3.78 (m, 2H, CHC$\underline{H}_2$), 5.75 (s, 2H, COC$\underline{H}_2$), 5.75 (br.s, 1H, $CH_2C\underline{H}$), 7.65 (s, 1H, ph-C$\underline{H}$), 6.88–7.93 (m, 13H, Ar–$\underline{H}$), 10.73 (s, 1H, N$\underline{H}$), 12.98 (s, 1H, COO$\underline{H}$). MS *m/z* 557 (M + 1). Anal. Calcd. for $C_{30}H_{24}N_2O_5S_2$: C, 64.73; H, 4.35; N, 5.03. Found: C, 64.56; H, 4.44; N, 5.17.

*5.8.12. (S,Z)-3-(1H-indol-3-yl)-2-(5-(4-(2-(3-methoxyphenyl)-2-oxoethoxy)benzyliden-e)-4-oxo-2-thioxothiazolidin-3-yl)propanoic acid (**V-l**)*

Yield 55%; m.p. 123–124 °C. IR (KBr) cm^{-1}: 3423 (OH), 3047 (NH), 1696 (C=O). ^1H NMR (DMSO-d_6, 300 MHz, ppm): δ 3.57–3.74 (m, 2H, CHC$\underline{H}_2$), 3.82 (s, 3H, OC$\underline{H}_3$), 5.71 (s, 2H, COC$\underline{H}_2$), 5.72 (br.s, 1H, $CH_2C\underline{H}$), 7.70 (s, 1H, ph-C$\underline{H}$), 6.86–7.70 (m, 13H, Ar–$\underline{H}$), 10.77 (s, 1H, N$\underline{H}$), 13.06 (s, 1H, COO$\underline{H}$). MS *m/z* 573 (M + 1). Anal. Calcd. for $C_{30}H_{24}N_2O_6S_2$: C, 62.92; H, 4.22; N, 4.89. Found: C, 63.16; H, 4.01; N, 4.93.

*5.8.13. (S,Z)-3-(1H-indol-3-yl)-2-(5-(4-(2-(4-methoxyphenyl)-2-oxoethoxy)benzyliden-e)-4-oxo-2-thioxothiazolidin-3-yl)propanoic acid (**V-m**)*

Yield59%; m.p. 116–118 °C. IR (KBr) cm^{-1}: 3424 (OH), 3047 (NH), 1695 (C=O). ^1H NMR (DMSO-d_6, 300 MHz, ppm): δ 3.57–3.85 (m, 2H, CHC$\underline{H}_2$), 3.85 (s, 3H, OC$\underline{H}_3$), 5.64 (s, 2H, COC$\underline{H}_2$), 5.65 (br.s, 1H, $CH_2C\underline{H}$), 7.67 (s, 1H, ph-C$\underline{H}$), 6.89–8.01 (m, 13H, Ar–$\underline{H}$), 10.72 (s, 1H, N$\underline{H}$), 12.89 (s, 1H, COO$\underline{H}$). MS *m/z* 573 (M + 1). Anal. Calcd. for $C_{30}H_{24}N_2O_6S_2$: C, 62.92; H, 4.22; N, 4.89. Found: C, 63.06; H, 4.10; N, 4.97.

5.9. Evaluation of anti-bacterial activity in vitro

The micro-organisms used in the present study were *S. aureus* (*S. aureus RN* 4220, *S. aureus KCTC* 209, *S. aureus KCTC* 503), and *E. coli* (*E. coli* 1356). The strains of multidrug-resistant clinical isolates were methicillin-resistant *S. aureus* (*MRSA CCARM* 3167 and *MRSA CCARM* 3506) and quinolone-resistant *S. aureus* (*QRSA CCARM* 3505 and *QRSA CCARM* 3519). Clinical isolates were collected from various patients hospitalized in several clinics.

Test bacteria were grown to mid-log phase in Mueller–Hinton broth (MHB) and diluted 1000-fold in the same medium. The bacteria of 10^5 CFU/mL were inoculated into MHB and dispensed at 0.2 mL/well in a 96-well microtiter plate. As positive controls, oxacillin and norfloxacin were used. Test compounds were prepared in DMSO, the final concentration of which did not exceed 0.05%. A two-fold serial dilution technique [18] was used to obtain final concentrations of 64–0.5 μg/mL. The MIC was defined as the concentration of a test compound that completely inhibited bacteria growth during 24 h incubation at 37 °C. Bacteria growth was determined by measuring the absorption at 650 nm using a microtiter enzyme-linked immunosorbent assay (ELISA) reader. All experiments were carried out three times.

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