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Green synthesis of 4-methoxybenzylidene thiazole derivatives using potassium carbonate as base under ultrasound irradiation

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A B S T R A C T

An environmentally benign aqueous protocol for the synthesis of novel 2-((5-(4-methoxybenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)amino)substituted acid by using potassium carbonate as a base has been achieved. These ultrasound irradiation and conventional technique reaction proceed efficiently in water in the absence of organic solvent. In comparison with conventional methods, our protocol is convenient and offers several advantages, such as shorter reaction time, higher yields, milder conditions and environmental friendliness.

1. Introduction

The Nitrogen-containing five and six-member heterocyclic compounds and their derivatives, which can be easily synthesized in laboratories, are particularly important and often found in natural sources. The 2-thioxothiazolidin-4-one (Rhodanine) based molecules and thiazole have been reported to exhibit a broad spectrum of biological activities, such as anti-inflammatory,[1,2] antipyretic,[3,4] antidiabetic,[5] anticancer,[6] antitubercular,[7,8] anti-HIV,[9-11] antiparasitic,[12] hypnotic[13] and antiproliferative agents.[14,15] Rhodanine was discovered in 1877, so there have been several attempts to design antimicrobial agents based on this heterocycles. There are various reports available on rhodanine derivatives as antimicrobial agents.[16-21] These reports suggested that a chain containing free carboxyl group at rhodanine nuclei was important to the observed levels of biological activity[22] and synthesized structures of rhodanine containing moiety is shown (**Fig. 1**).

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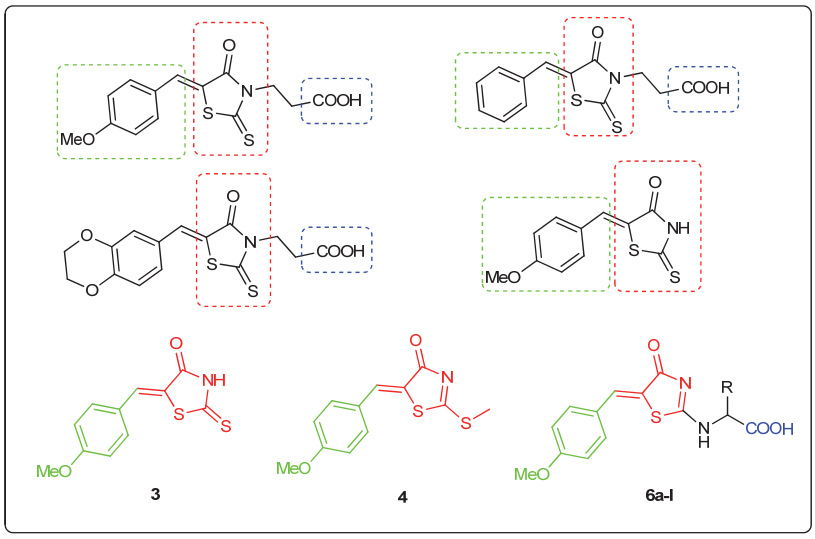


Fig. 1. Previously reported antimicrobial agents and synthesized compounds.

The most common protocol for the synthesis of thioxothiazolidinone involves active methylene group followed by intermolecular condensation with aromatic substituted aldehyde. However, these reactions required long reactions times, high temperatures, produce by-products, expensive reagents and, in general, have difficult purifications.[23-25] Ultrasound irradiation, an efficient and innocuous technique for reagent activation in the synthesis of organic compounds, and in particular heterocyclic compounds, has been applied with success, and generates products in good to excellent yields.[26-28] Ultrasound-promoted synthesis has attracted much attention during the past few decades. One advantage of using cavitation as an energy source to promote organic reactions includes shorter reaction times. Compared with conventional synthetic methods, the ultrasound- assisted method is reported as a fast, simple, convenient, time saving, economical, and environmentally benign method for the synthesis of novel materials.[29-31] It was known that the ultrasound agitation generate notable effects of chemical and physical effects due to the acoustic cavitation.[32,33] Ultrasonic irradiation has been acknowledged as an innocuous, green technique and its application today has been a boon in serving a new pathway for several chemical processes like reagent activation in the synthesis of organic and inorganic compounds.[34]

In view of the above considerations and in continuation of our previous work on thiazoles, thiazolidinones and sulphonamide derivatives of pharmaceutical interest,[35-47] we wish to report a simple, mild, competent and environmentally benign method for the synthesis and characterization of novel rhodanine derivatives **3**, **4** and **6a-l** by ultrasound irradiation and conventional technique via potassium carbonate catalyzed in water media.

2. Results and discussion

The synthetic protocols employed for the synthesis of rhodanine derivatives **3** and **4** presented in scheme 1, scheme 2 and **6a-l** are presented in scheme 3. The compound (*Z*)-5-(4-methoxybenzylidene)-2-thioxothiazolidin-4-one **3** was prepared via a Knoevenagel condensation between and 4-methoxybenzaldehyde (**1**) with rhodanine (**2**). The compound (*Z*)-5-(4-methoxybenzylidene)-2-(methylthio)thiazol-4(5H)-one **4** was obtained via reaction of the compound (**3**) with iodomethane in water using triethylamine as base.

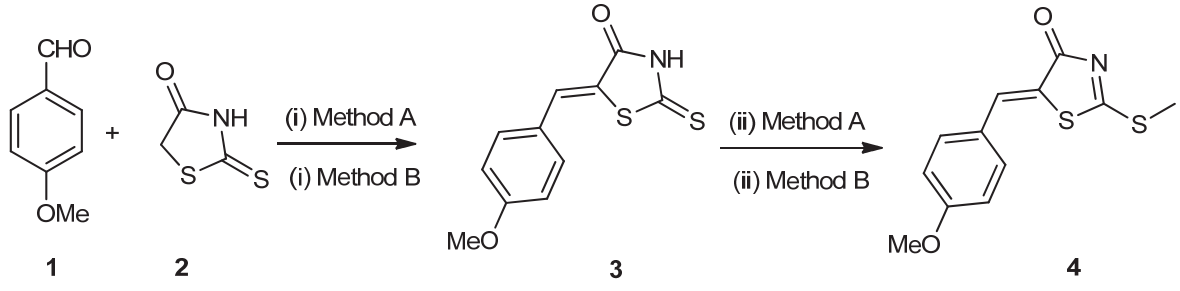
Table 1. Ultrasound irradiation: Screening of base, solvents, reaction time and yield for the synthesis (**6a**)[a]

Entry	Base	Solvent	Time (min)	Yield[b] (%)
1	Diethylamine	Water	12	62
2	Diethylamine	Methanol	18	32
3	Diethylamine	Acetic acid	15	32
4	Diethylamine	DCM	16	43
5	Diethylamine	Toluene	14	34
6	Triethylamine	Water	8	72
7	Triethylamine	Methanol	13	42
8	Triethylamine	Acetic acid	14	33
9	Triethylamine	DCM	12	44
10	Triethylamine	Toluene	18	36
11	Potassium carbonate	Water	1	99
12	Potassium carbonate	Methanol	12	72
13	Potassium carbonate	Acetic acid	10	73
14	Potassium carbonate	DCM	8	72
15	Potassium carbonate	Toluene	10	66

[a] All the reaction was carried out in equimolar amounts of each compound in 1 mL of solvent
[b] Isolated yield.

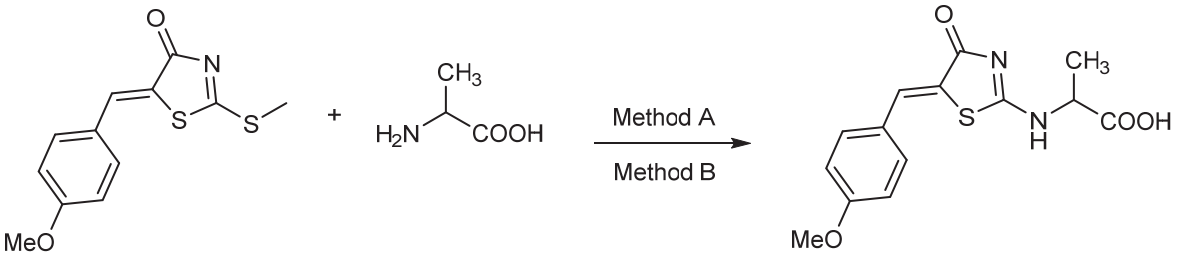
2.1. Effect of base and solvents

A variety of bases were screened under ultrasound irradiation in order to validate the right choice and the results are shown in Table 1. To justify the influence of the base, the reaction was carried out in the presence of base potassium carbonate wherein a maximum yield of 99% could be obtained (**Table 1**, Entry 11). It was further observed that the yield of the reaction hardly improved in the presence of other like diethylamine and triethylamine bases (**Table 1**, Entries 1 and 6), whereas the use of potassium carbonate as base significantly improved the yield to 99% (**Table 1**, Entry 11). Hence potassium carbonate under ultrasonic irradiation was selected for our further studies.



[a]Reaction condition: **(i) Method A:** Ultrasound irradiation: Sodium acetate, Acetic acid, 25 ºC, 25 min. **(i) Method B:** Conventional method: Sodium acetate, Acetic acid, reflux, 2 h. **(ii) Method A:** Ultrasound irradiation: Triethylamine, Iodomethane, Water, rt, 3 min. **(ii) Method B:** Conventional method: Triethylamine, Iodomethane, Water, rt, 1 h.

Scheme 1. Synthesis of (*Z*)-5-(4-methoxybenzylidene)-2-(methylthio)thiazol-4(5H)-one (**4**)[a]



4 **5a** **6a-l**

[a]Reaction condition: **Method A:** Ultrasound irradiation: Compound **4** (1 mmol), L-Alanine (**5a**) (1.2 mmol), base (1 mmol), solvent 1 mL, rt. 1-18 min. **Method B:** Conventional method: Compound **4** (1 mmol), L-Alanine (**5a**) (1.2 mmol), base (1 mmol), solvent 1 mL, rt. 10-98 min.

Scheme 2. Screening of model reaction (*Z*)-2-((5-(4-methoxybenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)amino)propanoic acid (**6a**)[a]

We synthesized and screening of model reaction under ultrasound irradiation and conventional method of the compound (*Z*)-2-((5-(4-methoxybenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)amino) propanoic acid **6a** (Scheme 2, Table 1, Table 2). The reaction in which the compound **4** (1 mmol) and the compound **5a** (1.2 mmol), various base and various solvents were selected as a model reaction to optimize the reaction conditions. In terms of the effect of solvents and base on the condensation reaction, potassium carbonate was found to be the better base and water was found to be the best solvent for the reaction (Table 1, entry 11); other solvents, including methanol, acetic acid, dichloromethane (DCM) and toluene were less efficient (Table 1, entries 2–5, 7–10 and 12–15).

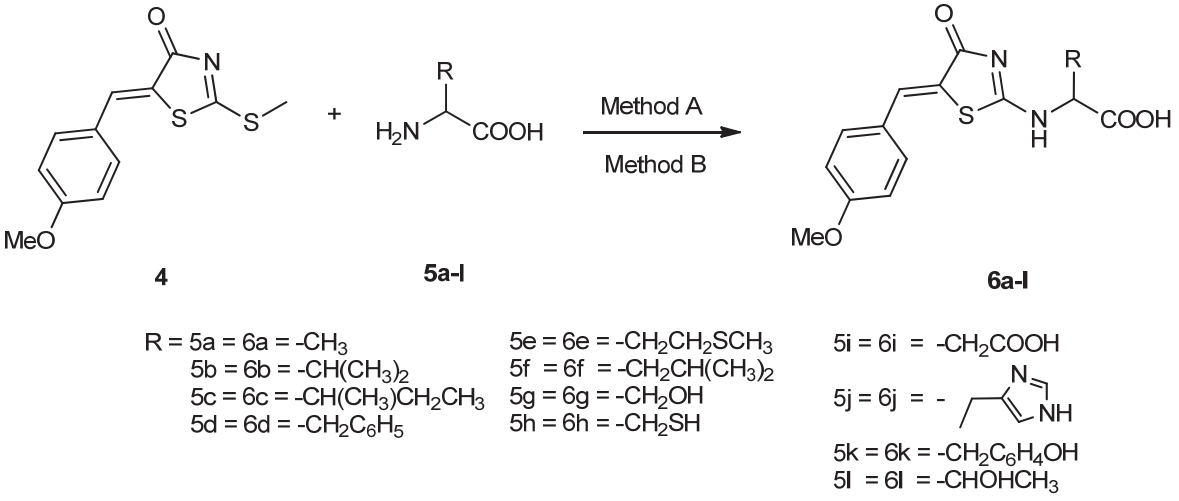
Table 2. Conventional method: Screening of base, solvents, reaction time and yield for the synthesis (**6a**)[a]

Entry	Base	Solvent	Time (min)	Yield[b] (%)
1	Diethylamine	Water	80	58
2	Diethylamine	Methanol	90	30
3	Diethylamine	Acetic acid	95	35
4	Diethylamine	DCM	98	40
5	Diethylamine	Toluene	92	30
6	Triethylamine	Water	82	68
7	Triethylamine	Methanol	84	40
8	Triethylamine	Acetic acid	86	30
9	Triethylamine	DCM	84	45
10	Triethylamine	Toluene	88	35
11	**Potassium carbonate**	**Water**	**10**	**88**
12	Potassium carbonate	Methanol	40	79
13	Potassium carbonate	Acetic acid	44	76
14	Potassium carbonate	DCM	46	78
15	Potassium carbonate	Toluene	48	68

[a] All the reaction was carried out in equimolar amounts of each compound in 1 mL of solvent
[b] Isolated yield.

Water gave the corresponding product in 62–99% yield, which was the best among these solvents (**Table 1**, entries 1, 6 and 11). To increase the efficiency of the condensation reaction, the effects of different base were investigated (Table 1, entries 1–15). Potassium carbonate exhibited the best performance with used solvents and gave better yield, (Table 1, entries 11–15). Sodium acetate and triethylamine gave lower yields with other solvents, but gave better yield in water as a solvent (Table 1, entries 1 and 6). All the reactions were carried out in equimolar amounts of each compound in 1 mL

of solvent. Among these reactions same amounts of the solvent, namely 1 mL of water turned out to be the best choice with yields of 62%, 72% and 99% (**Table 1**, entries 1, 6 and 11).

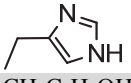


[a]Reaction condition: **Method A:** Ultrasound irradiation: potassium carbonate, water, rt, 1-4 min. **Method B:** Conventional: potassium carbonate, water, rt, 10-30 min.

Scheme 3. Synthesis of (*Z*)-2-((5-(4-methoxybenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)amino) substituted acid (**6a-l**).[a]

We also synthesized and screening of model reaction under conventional method and the results of these findings are presented in **Table 2**. The reaction in which the compound **4** (1 mmol) and the compound **5a** (1.2 mmol), various base and various solvents were selected as a model reaction to optimize the reaction conditions. In terms of the effect of solvents and base on the condensation reaction, potassium carbonate was found to be the better base and water was found to be the best solvent for the reaction (**Table 2**, entry 11); other solvents, including methanol, acetic acid, DCM and toluene were less efficient (**Table 2**, entries 2–5, 7–10 and 12–15). Nevertheless, all of these yields were generally low before further optimizations. Water gave the corresponding product in 58–88% yield, which was the best among these solvents (**Table 2**, entries 1, 6 and 11).

Table 3. Physical data for synthesized rhodanine derivatives **6(a-l)**[a]

Sr. No.	Substituent (R)	Time (min)		Yield[b] (%)		Melting point (°C)
		Ultrasound irradiation	Conventional method	Ultrasound irradiation	Conventional method	
6a	-CH_3	1	10	99	88	220-222
6b	-$CH(CH_3)_2$	1	30	98	85	212-214
6c	-$CH(CH_3)CH_2CH_3$	2	25	98	88	148-150
6d	-$CH_2C_6H_5$	2	25	97	88	178-180
6e	-$CH_2CH_2SCH_3$	3	25	98	92	176-178
6f	-$CH_2CH(CH_3)_2$	3	30	98	90	238-240
6g	-CH_2OH	4	25	97	88	241-243
6h	-CH_2SH	4	28	96	90	256-258
6i	-CH_2COOH	4	25	97	90	173-175
6j		2	30	98	90	198-200
6k	-$CH_2C_6H_4OH$	2	25	98	88	157-159
6l	-$CHOHCH_3$	3	22	98	82	181-183

[a]Reaction condition (**6a-l**). Compound (**4**) (1 mmol), amino acids (**5a-l**) (1.2 mmol),
Method A: Ultrasound irradiation: potassium carbonate, Water, rt, 1-4 min.
Method B: Conventional method: potassium carbonate, Water, rt, 10-30 min.
[b]Isolated yields

To increase the efficiency of the condensation reaction, the effects of different base were investigated (**Table 2**, entries 1–15). Potassium carbonate exhibited the best performance with used solvents and gave better yield, (**Table 2**, entries 11–15). Sodium acetate and triethylamine gave lower yields with other solvents, but gave better yield in ethanol as a solvent (**Table 2**, entries 1 and 6). All the reactions were carried out in equimolar amounts of each compound in 1 mL of solvent. Among these reactions same amounts of the solvent, namely 1 mL of ethanol turned out to be the best choice with yields of 58%, 68% and 88% (**Table 2**, entries 1, 6 and 11).

We would like to mention here that water as a solvent with potassium carbonate as base was the best choice with a yield of 99% and less time required for the completion of the reaction (**Table 1**, entry 11). Thus we decided to carry out the further reactions in water as a solvent with potassium carbonate as a base. As a result the reaction time was shortened; thermal decomposition was also minimized, at room temperature stirring, resulting in higher isolated yields. But in this synthesis, we compared to the reaction between ultrasound irradiation and conventional method, the ultrasound irradiation is the best method. Because the studies indicated that the use of ultrasound irradiation made the reactions very fast, very less time required to complete the reaction, and recorded high product yields 62%, 72% and 99% (**Table** 1, entries 1, 6 and 11) and surprisingly, in the conventional method, the reactions very sluggish and recorded low yields 58%, 68% and 88% (**Table 2**, entries 1, 6 and 11).

The physical data of the synthesized compounds are presented in **Table 3**. All the reactions proceeded well in 1-4 min to give products in very good yields (96–99%) by ultrasound irradiation and in conventional method, the reactions proceeded in 10-30 min to give products in yields (82–90%). The purity of the synthesized compounds was checked by TLC on silica gel precoated F254 Merck plates and melting points were recorded on SRS Optimelt, melting point apparatus and are uncorrected. The structure of the synthesized compounds was confirmed by IR, ^{1}H NMR, ^{13}C NMR and Mass spectral analysis.

3. Conclusions

With the pervasive applicability and pharmacoactivity of these derivatives, we have herein devised an energy efficient, general, cost effective and eco sustainable method for the synthesis of a series of rhodanine derivatives **3**, **4** and **6a-l**. The promising salient features of this strategy are absence of toxic organic solvents, minimization of waste, ease of product isolation, rapid, avoids laborious column purification steps, economically viable, easy to operate, rate and yield enhancements. The present method will permit a further increase of the diversity within rhodanine derivatives. It is envisaged that, the utility of sonication in combination with water as solvent and potassium carbonate as a base will make further development and good prospects for industrial application, synthetic chemistry and chemical science.

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4. Experimental section

4.1. Material and methods

Rhodanine, 4-methoxybenzaldehyde, anhydrous sodium acetate, triethylamine, dichloromethane, iodomethane and various solvents were commercially available. The major chemicals were purchased

from Sigma Aldrich and Avra labs. 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 on a FT-IR (Bruker). Melting points were recorded on SRS Optimelt, melting point apparatus and are uncorrected. The Ultrasonic Bath, sonicator of PCI Analytics having ultrasound cleaner with a frequency of 35 kHz and constant frequency 100 W maintained at 25ºC by circulating water. ^{1}H NMR spectra were recorded on a 400 MHz Varian NMR spectrometer and DMSO solvent is used. The following abbreviations are used; singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m) and broad (br). Mass spectra were taken with Micromass-QUATTRO-II of WATER mass spectrometer.

4.2. General procedure for the synthesis of compounds (3)

4.2.1. Method A: Ultrasound irradiation

A 50 mL flask was charged with 4-methoxybenzaldehyde **1** (1 mmol), 2-thioxothiazolidin-4-one **2** (1 mmol), anhydrous sodium acetate (1 mmol), acetic acid (1 mL). The mixture was sonicated (35 kHz, constant frequency) at 25 ºC for 25 min. The progress of the reaction was monitored by TLC (20% ethyl acetate: *n*-hexane). After completion of the reaction, the reaction mixture was poured into the ice-cold water. The precipitate was filtered off and washed with water (3×10 mL), dried and purified by recrystallized in ethanol as solvent to give 98 % yield.

4.2.2. Method B: Conventional method

A 50 mL round bottom flask, an equimolar amount of 4-methoxybenzaldehyde **1** (1 mmol), 2-thioxothiazolidin-4-one **2** (1 mmol), anhydrous sodium acetate (1 mmol) and acetic acid (1 mL) were added. The mixture was stirred under reflux condition for 2 h. The progress of the reaction was monitored by TLC (20% ethyl acetate: *n*-hexane). After completion of the reaction, the reaction mixture was poured into the ice-cold water. The precipitate was filtered off and washed with water (3×10 mL), dried and purified by recrystallized in ethanol as solvent to give 82 % yield.

4.2.2.1. ***(Z)-5-(4-methoxybenzylidene)-2-thioxothiazolidin-4-one (3)***

Yellow solid, Yield: 95%. mp 247–249 ºC; ES-MS m/z: 251.32. IR νmax/cm^{-1}: 3082 (NH), 1729 (C=O), 1575 (C=C), 1442 (C=N), 1277 (C=S), 1194(C–N). ^{1}H NMR (400 MHz, DMSO-d6, ppm) = 3.90 (s, 3H, OCH_3), 6.60–6.62 (d, J = 7.2 Hz, 2H, Ar–CH), 7.30–7.32 (d, J = 7.2 Hz, 2H, Ar–CH), 7.70 (s, 1H, =CH), 13.70 (s, 1H, NH). ^{13}C NMR: δppm = 55.8, 114.3, 116.0, 130.7, 142.9, 143.4, 160.5, 168.4, 193.7.

4.2.3. ***General procedure for the synthesis of compounds (4)***

4.2.3.1. Method A: Ultrasound irradiation

A 50 mL flask was charged with, the compound *(Z)-5-(4-methoxybenzylidene)-2-thioxothiazolidin-4-one* **3** (1 mmol), triethylamine (1.2 mmol), iodomethane (1.2 mmol) and water (1 mL). The mixture was sonicated (35 kHz, constant frequency) at 25 ºC for 3 min. The progress of the reaction was monitored by TLC (10% methanol: chloroform). After completion of the reaction, the reaction mixture was concentrated in-vacuo. The residue was washed with water (3×15 mL) to afford the crude product. The crude product was recrystallized using ethanol as solvent to give yield in the range 95%.

4.2.3.2. Method B: Conventional method

In a 50 ml round bottom flask, the compound (Z)-5-(4-methoxybenzylidene)-2-thioxothiazolidin-4-one **3** (1 mmol), triethylamine (1.2 mmol), iodomethane (1.2 mmol), water (1 mL) stirred at room

temperature up to 2 h. The progress of the reaction was monitored by TLC (10% methanol: chloroform). After completion of the reaction, the reaction mixture was concentrated in-vacuo. The residue was washed with water (3×15 mL) to afford the crude product. The crude product was recrystallized using ethanol as solvent to give yield in the range 85 %.

4.2.3.2.1. **(Z)-5-(4-methoxybenzylidene)-2-(methylthio)thiazol-4(5H)-one (4)**

Yellow solid, Yield: 95%. mp 162–164 ºC; ES-MS m/z: 265.35. IR νmax/cm^{-1}: 1681 (C=O), 1572 (C=C), 1503 (C=N), 1149 (C-S), 911 (C–N). ^{1}H NMR (400 MHz, DMSO-d6, ppm)= 2.80 (s, 3H, S-CH_3), 3.80 (s, 3H, OCH_3), 6.70–6.72 (d, 2H, Ar–CH), 7.30–7.32 (d, 2H, Ar–CH), 7.90 (s, 1H, =CH). ^{13}C NMR: δppm = 14.4, 55.8, 114.2, 127.5, 130.5, 132.6, 152.3, 160.1, 162.7, 167.2.

4.3. ***General procedure for the synthesis of (Z)-2-((5-(4-methoxybenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)amino)substituted acid (6a-l)***

4.3.1. Method A: Ultrasound irradiation:

A 50 mL flask was charged with, the compound (*Z*)-5-(4-methoxybenzylidene)-2-(methylthio)thiazol-4(5H)-one **4** (1 mmol), amino acids **5a-l** (1.2 mmol), potassium carbonate (1 mmol) and water (1 mL). The mixture was sonicated (35 kHz, constant frequency) at 25 ºC for 1-4 min. The progress of the reaction was monitored by TLC (10% methanol: chloroform). After completion of the reaction, the reaction mixture was concentrated in-vacuo. The residue was washed with water (3×15 mL) to afford the crude product. The compounds (*Z*)-2-((5-(4-methoxybenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)amino) substituted acid **6a-l** were recrystallized from ethanol and isolated as yellowish solids.

4.3.2. Method B: Conventional method:

In a 50 ml round bottom flask, the compound (*Z*)-5-(4-methoxybenzylidene)-2-(methylthio)thiazol-4(5H)-one **4** (1 mmol), amino acids **5a-l** (1.2 mmol), potassium carbonate (1 mmol) and water (1 mL) were added to the reaction mixter and stirred for 10-30 min at room temperature. The progress of the reaction was monitored by TLC (10% methanol: chloroform). After completion of the reaction, the reaction mixture was concentrated in-vacuo. The residue was washed with water (3×15 mL) to afford the crude product. The compounds (*Z*)-2-((5-(4-methoxybenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)amino) substituted acid **6a-l** were recrystallized from ethanol and isolated as yellowish solids.

4.3.2.1. ***(Z)-2-((5-(4-methoxybenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)amino)propanoic acid (6a)***

Yellow solid, Yield: 99%, mp 220–222 ºC; ES-MS m/z: 306.34. IR νmax /cm^{-1}: 3384 (OH), 2657 (CH–Ar), 1737 (HO–C=O), 1690 (C=O), 1599(C=C), 1553 (C=N), 1006 (C-S), 761 (C–N). ^{1}H NMR (400 MHz, DMSO-d6, ppm) = 1.30–1.32 (d, 3H, CH_3), 3.80 (s, 3H, OCH_3), 4.50–4.52 (q, 1H, CH), 7.50–7.70 (m, 4H, Ar–CH), 7.80 (s, 1H, =CH), 8.40 (s, 1H, NH), 10.15 (s, 1H, COOH). ^{13}C NMR: δppm = 16.8, 53.5, 55.5, 56.2, 114.1, 130.4, 132.5, 143.4, 152.3, 158.6, 160.7, 167.7, 174.2.

4.3.2.2. ***(Z)-2-((5-(4-methoxybenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)amino)-3-methyl butanoic acid (6b)***

Yellow solid, Yield: 98%, mp 212–214 ºC; ES-MS m/z: 334.39. IR νmax /cm^{-1}: 3744 (OH), 3011 (NH), 1737 (HO–C=O), 1689 (C=O), 1553 (C=C), 1509 (C=N), 1232 (C-S), 1010 (C–N). ^{1}H NMR (400 MHz, DMSO-d6, ppm) = 0.90–0.92 (d, 6H, CH_3), 2.20–2.22 (m, 1H, CH), 3.80 (s, 3H, OCH_3), 4.50–4.52 (d, 1H, CH), 7.40–7.42 (d, *J* = 7.2 Hz, 2H, Ar–CH), 7.60–7.62 (d, *J* = 7.2 Hz, 2H, Ar–CH),

7.80 (s, 1H, =CH), 10.02 (s, 1H, NH), 13.15 (s, 1H, COOH). ^{13}C NMR: δppm = 18.2, 30.1, 55.6, 61.3, 114.3, 127.6, 130.7, 132.4, 153.3, 157.6, 161.7, 168.7, 174.4.

4.3.2.3. ***(Z)-2-((5-(4-methoxybenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)amino)-3-methyl pentanoic acid (6c)***

Yellow solid, Yield: 98%, mp 148–150 ºC; ES-MS m/z: 348.42. IR νmax/cm^{-1}: 3624 (OH), 3563 (NH), 2969 (Ar-CH), 1730 (HO–C=O), 1641 (C=O), 1609 (C=C), 1584 (C=N), 1183 (C-S), 1093 (C–N). ^{1}H NMR (400 MHz, DMSO-d6, ppm) = 1.10–1.12 (m, 8H, CH_2CH_3), 1.30–1.32 (m, 1H, CH), 3.20–3.22 (d, 1H, CH), 3.70 (s, 3H, OCH_3), 7.40–7.42 (d, *J* = 7.6 Hz, 2H, Ar–CH), 7.90 (s, 1H, =CH), 8.20 (d, *J* = 7.6 Hz, 2H, Ar–CH), 8.80 (s, 1H, NH), 10.30 (s, 1H, COOH). ^{13}C NMR: δppm = 11.2, 15.2, 25.2, 37.5, 55.3, 55.6, 56.2, 55.8, 130.6, 132.7, 143.4, 152.3, 161.7, 167.7, 174.6.

4.3.2.4. ***(Z)-2-((5-(4-methoxybenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)amino)-3-phenyl propanoic acid (6d)***

Yellow solid, Yield: 97%, mp 178–180 ºC; ES-MS m/z: 382.43. IR νmax /cm^{-1}: 3392 (OH), 3210 (NH), 2976 (CH–Ar), 1730 (HO–C=O), 1699 (C=O), 1563 (C=C), 1544 (C=N), 1012 (C-S), 1068 (C–N). ^{1}H NMR (400 MHz, DMSO-d6, ppm) = 2.50–2.52 (d, 2H, CH_2), 3.80 (s, 3H, OCH_3), 4.40–4.42 (q, 1H, CH), 7.20–7.70 (m, 9H, Ar–CH), 7.90 (s, 1H, =CH), 9.14 (s, 1H, NH), 11.02 (s, 1H, COOH). ^{13}C NMR: δppm = 55.4, 56.2, 36.4, 58.4, 114.5, 125.9, 127.7, 128.6, 128.9, 135.3, 136.9, 143.4, 152.2, 158.5, 167.2, 174.2.

4.3.2.5. ***(Z)-2-((5-(4-methoxybenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)amino)-4-(methylthio) butanoic acid (6e)***

Yellow solid, Yield: 98%, mp 176–178 ºC; ES-MS m/z: 366.46. IR νmax /cm^{-1}: 3475 (OH), 3213 (NH), 2922 (CH–Ar), 1719 (HO–C=O), 1699 (C=O), 1582 (C=C), 1452 (C=N), 1215 (C-S), 1029 (C–N). ^{1}H NMR (400 MHz, DMSO-d6, ppm) = 2.10 (s, 3H, CH_3), 2.30–2.32 (q, 2H, CH_2), 2.60–2.62 (t, 2H, CH_2), 3.30–3.32 (q, 1H, CH), 3.80 (s, 3H, OCH_3), 7.10–7.12 (d, *J* = 7.2 Hz, 2H, Ar–CH), 7.50–7.52 (d, *J* = 7.2 Hz, 2H, Ar–CH), 7.80 (s, 1H, =CH), 9.30 (s, 1H, NH), 10.20 (s, 1H, COOH). ^{13}C NMR: δppm = 15.2, 29.2, 30.5, 55.4, 56.6, 56.8, 114.6, 130.4, 132.3, 143.5, 152.3, 161.7, 167.7, 174.6.

4.3.2.6. ***(Z)-2-((5-(4-methoxybenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)amino)-4-methyl pentanoic acid (6f)***

Yellow solid, Yield: 98%, mp 238–240 ºC; ES-MS m/z: 348.44. IR νmax /cm^{-1}: 3382 (OH), 3212 (NH), 3020 (CH–Ar), 1721 (HO–C=O), 1699 (C=O), 1515 (C=C), 1574 (C=N), 1023 (C-S), 1051 (C–N). ^{1}H NMR (400 MHz, DMSO-d6, ppm) = 0.92–0.94 (d, 6H, CH–$(CH_3)_2$), 1.42–1.44 (m, 1H, CH), 1.70–1.72 (t, 2H, CH_2), 3.82 (s, 3H, OCH_3), 4.40–4.42 (q, 1H, CH), 7.20–7.22 (d, *J* = 7.2 Hz, 2H, Ar–CH), 7.50–7.52 (d, *J* = 7.2 Hz, 2H, Ar–CH), 7.80 (s, 1H, =CH), 9.20 (s, 1H, NH), 11.84 (s, 1H, COOH). ^{13}C NMR: δppm = 22.8, 24.5, 40.1, 55.2, 55.8, 114.2, 127.2, 130.1, 132.4, 152.2, 158.1, 160.1, 167.1, 174.2.

4.3.2.7. ***(Z)-2-((5-(4-methoxybenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)amino)-3-hydroxy propanoic acid (6g)***

Yellow solid, Yield: 97%, mp 241–243 ºC; ES-MS m/z: 332.34. IR νmax /cm^{-1}: 3420 (OH), 3211 (NH), 3017 (CH–Ar), 1730 (HO–C=O), 1698 (C=O), 1543 (C=C), 1521 (C=N), 1029 (C-S), 1097 (C–N). ^{1}H NMR (400 MHz, DMSO-d6, ppm) = 3.60 (t, 1H, CH), 3.85 (s, 3H, OCH_3), 4.01–4.03 (d, 2H, CH_2), 5.30 (s, 1H, OH), 7.10–7.12 (d, 2H, Ar–CH), 7.30 (d, 2H, Ar–CH), 7.78 (s, 1H, =CH), 9.12 (s,

1H, NH), 10.86 (s, 1H, COOH). ^{13}C NMR: δppm = 55.5, 59.2, 62.3, 114.8, 127.1, 132.9, 135.1, 151.9, 158.1, 159.6, 167.9, 171.2.

4.3.2.8. ***(Z)-2-((5-(4-methoxybenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)amino)-3-mercapto propanoic acid (6h)***

Yellow solid, Yield: 96%, mp 256–258 ºC; ES-MS m/z: 338.40. IR νmax /cm^{-1}: 3415 (OH), 3211 (NH), 3011 (CH–Ar), 2510 (SH), 1735 (HO–C=O), 1698 (C=O), 1559 (C=C), 1501 (C=N), 1011 (C-S), 1099 (C–N). ^{1}H NMR (400 MHz, DMSO-d6, ppm) = 1.40 (s, 1H, SH), 3.10–3.12 (d, 2H, CH_2), 3.82 (s, 3H, OCH_3), 4.15–4.17 (t, 1H, CH), 7.02–7.04 (d, *J* = 7.6 Hz, 2H, Ar–CH), 7.42–7.44 (d, *J* = 7.6 Hz, 2H, Ar–CH), 7.78 (s, 1H, =CH), 9.88 (s, 1H, NH), 11.54 (s, 1H, COOH). ^{13}C NMR: δppm = 26.9, 55.2, 60.5, 114.7, 128.8, 130.1, 132.5, 143.6, 152.9, 158.3, 167.2, 178.2.

4.3.2.9. ***(Z)-2-((5-(4-methoxybenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)amino)succinic acid (6i)***

Yellow solid, Yield: 97%, mp 173–175 ºC; ES-MS m/z: 350.37. IR νmax /cm^{-1}: 3426 (OH), 3210 (NH), 3016 (CH–Ar), 1732 (HO–C=O), 1705 (C=O), 1532 (C=C), 1511 (C=N), 1014 (C-S), 1040 (C–N). ^{1}H NMR (400 MHz, DMSO-d6, ppm) = 2.61–2.63 (d, 2H, CH_2), 3.71–3.73 (t, 1H, CH), 3.90 (s, 3H, OCH_3), 7.12–7.14 (d, *J* = 7.2 Hz, 2H, Ar–CH), 7.52–7.54 (d, *J* = 7.2 Hz, 2H, Ar–CH), 7.78 (s, 1H, =CH), 9.70 (s, 1H, NH), 11.74 (s, 2H, COOH). ^{13}C NMR: δppm = 35.9, 53.2, 55.3, 114.7, 127.5, 128.8, 132.5, 135.6, 152.9, 158.3, 167.2, 172.2, 178.2.

4.3.2.10. ***(Z)-2-((5-(4-methoxybenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)amino)-3-(1H-imidazol-4-yl)propanoic acid (6j)***

Yellow solid, Yield: 98%, mp 198–200 ºC; ES-MS m/z: 372.40. IR νmax /cm^{-1}: 3442 (OH), 3296 (NH), 2921 (CH–Ar), 1693 (C=O), 1500 (C=C), 1455 (C=N), 1015 (C-S), 824 (C–N). ^{1}H NMR (400 MHz, DMSO-d6, ppm) = 3.10 (s, 2H, CH_2), 3.60 (s, 1H, CH), 3.82 (s, 3H, OCH_3),), 7.10–7.12 (d, *J* = 7.2 Hz, 2H, Ar–CH), 7.30–7.32 (d, *J* = 7.2 Hz, 2H, Ar–CH), 7.64 (s, 1H, =CH *imidazole ring*), 7.80 (s, 1H, =CH), 8.64 (s, 1H, =CH *imidazole ring*), 8.70 (s, 2H, NH), 10.90 (s, 1H, COOH). ^{13}C NMR: δppm = 28.9, 58.3, 117.9, 55.2, 114.5, 124.7, 127.9, 128.4, 129.2, 132.1, 135.2, 152.3, 159.2, 168.5, 175.2.

4.3.2.11. ***(Z)-2-((5-(4-methoxybenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)amino)-3-(4-hydroxyphenyl) propanoic acid (6k)***

Yellow solid, Yield: 98%, mp 157–159 ºC; ES-MS m/z: 398.43. IR νmax /cm^{-1}: 3445 (O=C-OH), 3393 (OH), 3214 (NH), 2974 (CH–Ar), 1731 (HO–C=O), 1699 (C=O), 1543 (C=C), 1591 (C=N), 1011 (C-S), 1082 (C–N). ^{1}H NMR (400 MHz, DMSO-d6, ppm) = 2.80–2.82 (d, 2H, CH_2), 3.80 (s, 3H, OCH_3), 4.40–4.42 (t, 1H, CH), 5.32 (s, 1H, OH), 7.10–7.12 (d, *J* = 7.6 Hz, 4H, Ar–CH), 7.50–7.52 (d, *J* = 7.6 Hz, 4H, Ar–CH), 7.72 (s, 1H, =CH), 9.32 (s, 1H, NH), 11.16 (s, 1H, COOH). ^{13}C NMR: δppm = 36.4, 55.6, 56.6, 115.9, 127.7, 128.6, 128.9, 129.2, 130.2, 135.3, 152.2, 155.7, 158.5, 167.7, 174.2.

4.3.2.12. ***(Z)-2-((5-(4-methoxybenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)amino)-3-hydroxy butanoic acid (6l)***

Yellow solid, Yield: 98%, mp 181–183 ºC; ES-MS m/z: 336.36. IR νmax /cm^{-1}: 3454 (OH), 3212 (NH), 3012 (CH–Ar), 1733 (HO–C=O), 1691 (C=O), 1555 (C=C), 1597 (C=N), 1046 (C-S), 1112 (C–N). ^{1}H NMR (400 MHz, DMSO-d6, ppm) = 1.15–1.17 (d, 3H, CH_3), 3.50–3.52 (d, 1H, CH), 3.60 (s, 1H, OH), 3.80 (s, 3H, OCH_3), 3.93–3.95 (m, 1H, CH), 7.20–7.22 (d, *J* = 7.2 Hz, 2H, Ar–CH), 7.50–

7.652 (d, *J* = 7.2 Hz, 2H, Ar–CH), 7.74 (s, 1H, =CH), 9.68 (s, 1H, NH), 11.24 (s, 1H, COOH). ^{13}C NMR: δppm = 19.7, 55.6, 56.6, 64.4, 127.8, 128.7, 128.9, 132.4, 135.1, 152.9, 158.2, 167.8, 175.2.

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