Microwave Induced Synthesis of the Thiazolidine-2,4-dione Motif and the Efficient Solvent Free-Solid Phase Parallel Syntheses of 5-Benzylidene-thiazolidine-2,4-dione and 5-Benzylidene-2-thioxo-thiazolidine-4-one Compounds

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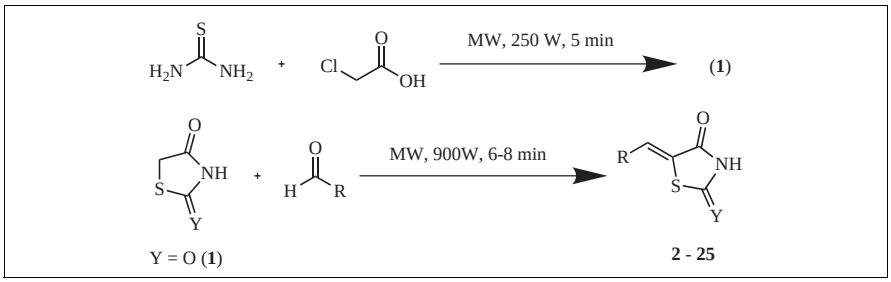

Novel microwave induced method for the synthesis of thiazolidine-2,4-dione motif under solvent phase conditions is developed. Further we report an efficient, microwave assisted method for the parallel syntheses of biologically important 5-benzylidene-thiazolidine-2,4-dione and 5-benzylidene-2-thioxo-thiazolidine-4-one compounds under solid-phase and solvent-free conditions. A comparative study between the developed microwave methods and the conventional methods is described. We have also illustrated the possible mechanism behind to address the reason why piperidine, acetic acid and silica gel enhanced the Knoevenagel condensation reaction.

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Introduction.

Various 1,3-thiazolidine derivatives have been reported for their diverse biological activities apart from synthetic interests [1-4]. Activities such as antibacterial [5], anti-inflammatory, cardiovascular, hypoglycaemic, lipid lowering [6,7] and various others have been reported [8]. Thiazolidine-2,4-dione derivative LY213829, developed for the treatment of inflammatory bowel disease [9] and Rosiglitasone, developed for the non-insulin dependant diabetes mellitus [10] contain thiazolidine-2,4-dione motif. All these compounds have a substitution on the active methylene group at the fifth position of the thiazolidine-2,4-dione motif.

The syntheses of these biologically active compounds involves the synthesis of thiazolidine-2,4-dione motif by reacting chloroacetic acid and thiourea using water as a solvent. The reaction mixture is stirred under ice cold conditions for 15 min, refluxed for 12 h and cooled to get white crystals of thiazolidine-2,4-dione. Further, the 5-benzylidene-thiazolidine-2,4-dione is synthesised by the condensation of corresponding aldehydes on to the fifth position of thiazolidine-2,4-dione motif having an active methylene group using toluene as solvent. This reaction is a Knoevenagel condensation reaction and it involves heating for 5-12 h or more depending on the nature and substitution on the aldehyde. Knoevenagel condensation reaction needs azeotropic removal of water molecules using Dean-Stark apparatus. To do this reaction in a parallel synthetic fashion becomes tedious under conventional method.

The Knoevenagel condensation reaction is time consuming for those involved in drug discovery process. There is no efficient method available to speed up the drug discovery process for loading diverse compound libraries of 5-benzylidene-1,3-thiazolidine derivatives to high throughput screening.

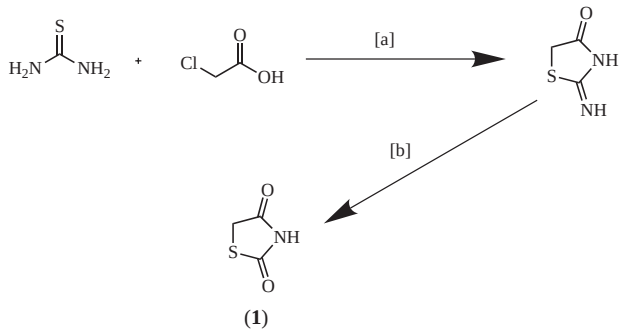
In the last decade, microwave promoted reactions under solid-phase, solvent-free conditions have been proved to be environmentally benign. It has received considerable attention as a powerful technique to effect various organic transformations [11-13].

In this article we wish to demonstrate the microwave assisted synthesis of thiazolidine-2,4-dione motif. Further, we also report derivetisation of thiazolidine-2,4-dione and its bioisoster, 2-thioxo-thiazolidine-4-one or rhodanine motifs by Knoevenagel condensation reaction in pollution free conditions. Our efforts have resulted in the development of new and efficient methods to synthesize the titled compounds. Many of the compounds synthesised were found to be novel as well.

Results and Discussion.

The heterocyclic motif thiazolidine-2,4-dione was synthesized in two steps with microwave assistance in the second step as shown in Scheme 1. Water was used as a solvent in this reaction.

Scheme 1



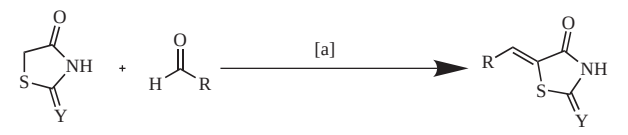
(**1**)

Preparation of thiazolidine-2,4-dione. [a] 0-5°C, water, stirring for 15 min. [b] MW 250W, 5 min.

The ^{1}H NMR spectra for thiazolidine-2,4-dione shows a singlet at 3.98(δ ppm) for $–CH_2$- protons and a broad singlet at 12.51 for NH proton. The reason for this desheilding is due to the presence of two electron-withdrawing carbonyl groups, on either side of NH group in the thiazolidine ring system. The power of microwave irradiation used for this reaction was 250W. Since the reactants and the solvent used in this reaction were highly polar having high dielectric constants. It was found difficult to avoid bumping of reaction mixtures during the microwave irradiation at the power of 700W and 500W.

Further, the thiazolidine-2,4-dione motif was derivatised at its fifth position by Knoevenagel condensation reaction. To perform this reaction, we have extended the classical Pechmann approach for the synthesis of coumarins to the microwave promoted [14,15], environmentally friendly, solid phase and solvent-free parallel synthesis of 5-benzylidene-thiazolidine-2,4-dione and 5-benzylidene-2-thioxo-thiazolidine-4-one compounds. To explore the scope of microwave assisted parallel synthesis; two series of compounds were synthesized according to Scheme 2 and are listed in the Table 1.

Scheme 2



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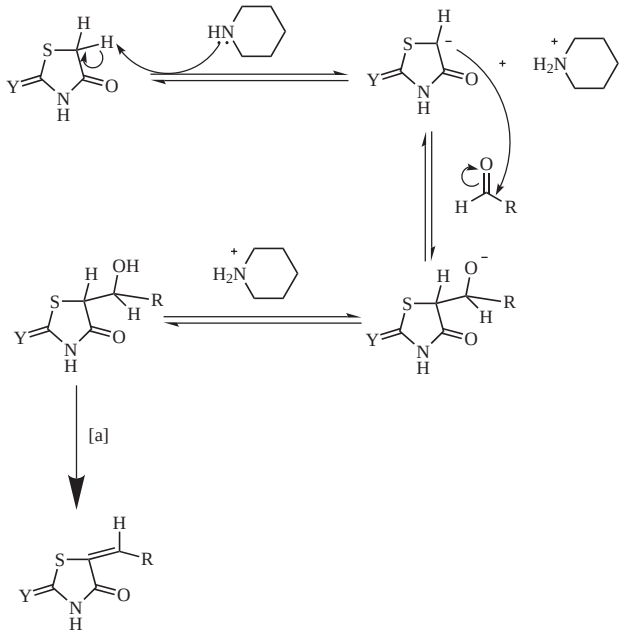
Knoevenagel condensation reactions; Y = O (**1**), Y = S (Rhodanine). [a] Piperidine, activated silica gel, acetic acid, MW 900W, 6-8 min.

The reaction times were greatly reduced. The method was simple to carry out with relatively good yields. The reactions can be scaled up to 3 g yield and the reactions were carried out in long necked glass tubes. The yields were greatly reduced when the reaction was performed in the absence of silica gel. The addition of acetic acid (0.01 mmol) after three minutes of microwave irradiation increased the yields, possibly by enhancing the rate of dehydration of alcohol or 1,2 elimination step which is the last step in Knoevenagel condensation reaction mechanism as outlined in Scheme 3. Dehydration of alcohol was known to be promoted in acidic conditions [16-18]. The corresponding 5-benzylidene products show a singlet peak for =CH Ar between 7.49 and 7.88 (δ ppm) in ^{1}H NMR spectrum.

Scheme 3

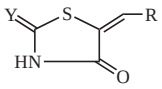


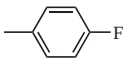
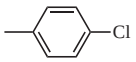
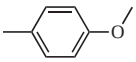
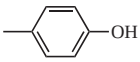
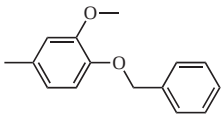
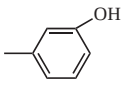
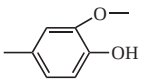
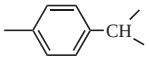
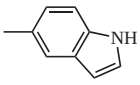
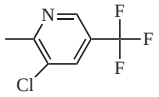
[a] 1,2-Elimination or dehydration possibly enhanced in presence of acetic acid as a catalyst.

To confirm the role of acetic acid we performed the above Knoevenagel condensation reactions using the same microwave method without the addition of acetic acid. But the yields were reduced. To compare and contrast, we performed the above reactions individually by conventional method. The comparative data for the reaction time and yield under both the conventional and microwave methods are as shown in Table 1. According to the literature [10], to synthesise compounds **2**, **6**, **8** and **14** they have refluxed individually each reaction mixture for 16 h with the azeotropic removal of water molecules using Dean-Stark apparatus.

Table 1

5-Benzylidene-thiazolidine-2,4-dione and 5-benzylidene-2-thioxo-thiazolidine-4-one compounds synthesized by microwave irradiation.



Product	R	Y	Reaction Time		Yield (%) [a]		
			MW [b] (min)	Conven (h)	MW with AcOH	MW without AcOH	Conven
2		O	7	13	87	83	83[c]
3		S	7	13	87	79	77
4		O	7	14	85	79	75
5		S	7	14	87	82	71
6		O	7	12	97	89	97[c]
7		S	7	12	91	90	90
8		O	8	14	90	89	88[c]
9		S	8	14	89	83	83
10		O	8	13	89	81	83
11		S	8	13	92	84	84
12		O	7	12	89	85	82
13		S	7	12	89	84	82
14		O	7	12	95	93	93[c]
15		S	7	12	95	92	91
16		O	8	12	89	84	74
17		S	8	12	87	78	73
18		O	7	12	85	82	82
19		S	7	12	86	84	85
20		O	8	12	87	84	84
21		S	8	12	89	83	82
22		O	8	12	80	78	76
23		S	8	12	82	75	74
24		O	6	13	81	73	65
25		S	6	13	85	75	64

[a] Isolated yield. [b] Microwave irradiation (BPL-SANYO^{TM} domestic microwave oven). [c] Literature reported yield [10].

In conclusion, we have demonstrated for the first time the microwave induced synthesis of thiazolidine-2,4-dione motif. Followed by this, we have also developed a microwave induced efficient method for the parallel synthesis of biologically important 5-benzylidene-thiazolidine-2,4-diones and 5-benzylidene-2-thioxo-thiazolidine-4-ones by Knoevenagel condensation reaction. Commercially available reagents and unmodified household microwave oven were used to develop the methods. Presence of acetic acid, silica gel and piperidine enhanced the Knoevenagel condensation.

The advantages of the present microwave methods are faster reaction rates, water is used as a solvent for the synthesis of thiazolidine-2,4-dione motif. Also no solvent is used in Knoevenagel condensation reactions irrespective of whether the aldehyde is liquid or solid making this method pollution free. Microwave method is a convenient and a simple method as compared to conventional method to perform parallel synthesis. In the conventional method to perform the above Knoevenagel condensation reactions requires Dean-Stark apparatus and toluene to serve as a solvent, whereas in the present microwave method activated silica gel does this job. Formation of cleaner products with relatively better yields under microwave method is another advantage. This protocol is, therefore, a valuable alternative to the conventional methods for the syntheses of these classes of compounds. We are now extending this technique for other classes of heterocyclic compounds containing active methylene groups. The results will be reported in our next publication.

EXPERIMENTAL

All the synthesised compounds were analyzed by different analytical procedures. TLC was performed using 4% methanol in chloroform as a mobile phase on aluminum plates precoated with silica gel GF to monitor the reactions. The melting points were determined in open capillaries and are uncorrected. ^{1}H NMR was recorded on a Bruker ACF-300 MHz spectrometer using DMSO-d_6 as a solvent and tetramethyl silane as internal standard. The chemical shifts are expressed in ppm and the following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. The mass spectrum was recorded using VG Quattro II (ESI with triple Quadra pole) mass spectrometer. Elemental analysis was performed to analyze three elements (Carbon, Hydrogen and Nitrogen) using CHNS-932 instrument (LECO Corprn, USA).

Procedure for the synthesis of thiazolidine-2,4-dione motif (**1**):

Chloroacetic acid (3 mmol) and thiourea (3 mmol) were transferred to a long necked glass vial. Water (20 mmol) was added and stirred under ice cold conditions (0-5 °C) for about 15 min to form a white precipitate of 2-imino-thiazolidine-4-one intermediate. Microwave irradiation was then carried out at 250W power for 5 min. Intermittent cooling was done for about one min after every 15 sec of microwave irradiation (because water is used as a solvent in this reaction it conducts microwaves greatly in the presence of highly polar chloroacetic acid). Then reaction mixture was cooled and the solid that separated was collected by filtration and washed with water to give white crystals of thiazolidine-2,4-dione (83% yield). The reaction was monitored through TLC at regular intervals. The yield was found to be the same both under conventional as well as microwave methods. Conventional method, however, required refluxing for 12 h.

General procedure for Knoevenagel condensation reaction (**2-25**):

Knoevenagel condensation reaction was carried out in a parallel synthetic route to produce two similar series of compounds containing different motifs as shown in Scheme 2 and Table 1. Each 3 mmol of thiazolidine-2,4-dione and thiazolidine-2-thioxo-thiazolidine-4-one or rhodanine were transferred to a 2 x 12 long necked glass vials in parallel. Piperidine (0.03 mmol) and activated silica gel (approximately 100 mg) to adsorb water molecules eliminated during the reaction were added to all the vials. Various aryl and heteryl aldehydes (3 mmol either solid or liquid) were then added. The vials containing reaction mixtures were thoroughly mixed and placed in a microwave oven in a circle.

Microwave irradiation was carried out at 900 W power for 6-8 min. Intermittent cooling was done after every 60 sec of microwave irradiation. During cooling, the reaction mixtures were thoroughly mixed. Acetic acid (0.01 mmol) was added to all the 24 reaction mixtures after three minutes of microwave irradiation.

The reaction mixtures were withdrawn from microwave oven soon after the reactions were completed based on TLC data at regular intervals and cooled to room temperature. The reaction mixtures were extracted with ethyl acetate (2×15 mL) and washed with 15 mL of water. The ethyl acetate layer was separated and dried over $MgSO_4$ and evaporated to obtain the products. The products obtained were purified by recrystallization with ethyl acetate and hexane mixture in the ratio 9:1.

Thiazolidine-2,4-dione (**1**).

This compound was obtained according to the above procedure for synthesis of thiazolidine-2,4-dione motif as a white crystals (83%); mp 123-125 °C; ^{1}H NMR: δ (ppm) 3.98 (s, 2H, CH_2), 12.51 (bs, 1H, NH); MS: m/z (%) found 116.2 (100), calcd 116 $(M-H)^-$.

Anal. Calcd. for $C_3H_3NO_2S$: C, 30.76; H, 2.58; N, 11.96. Found: C, 30.54 ; H, 2.71; N, 11.73.

(*Z*)-5-(4-Flurobenzylidene)-thiazolidine-2,4-dione (**2**).

This compound was obtained according to the above general procedure for Knoevenagel condensation reaction as orange crystals; mp 220-223 °C; ^{1}H NMR: δ (ppm) 7.40 (m, 2H, ArH), 7.71 (m, 2H, ArH), 7.81 (s, 1H, =CHAr), 12.65 (bs, 1H, NH); MS: m/z (%) found 222.0 (100), calcd 222 $(M-H)^-$. 152.0, 116.2, 106.0.

Anal. Calcd. for $C_{10}H_6FNO_2S$: C, 53.81; H, 2.71; N, 6.27. Found: C, 53.62; H, 2.83; N, 6.15.

(*Z*)-5-(4-Flurobenzylidene)-2-thioxo-thiazolidine-4-one (**3**).

This compound was obtained according to the above general procedure for Knoevenagel condensation reaction as yellow crystals; mp 217-219 °C; ^{1}H NMR: δ (ppm) 7.36 (m, 2H, ArH),

7.69 (m, 2H, ArH), 7.68 (s, 1H, =CHAr), 13.90(bs, 1H, NH). MS: m/z (%) found 238.0 (100), calcd 238 $(M-H)^-$. 189.2, 131.0, 106.0.

Anal. Calcd. for $C_{10}H_6FNOS_2$: C, 50.19; H, 2.53; N, 5.85. Found: C, 49.88; H, 2.61; N, 5.73.

(*Z*)-5-(4-Chlorobenzylidene)-thiazolidine-2,4-dione (**4**).

This compound was obtained according to the above general procedure for Knoevenagel condensation reaction as a white crystals; mp 255-257 °C; ^{1}H NMR: δ (ppm) 7.39 (m, 2H, ArH), 7.67 (m, 2H, ArH), 7.88 (s, 1H, =CHAr), 12.58 (bs, 1H, NH); MS: m/z (%) found 238.0 (100), calcd 238 $(M-H)^-$. (M-H)+2 (37.21%, 1 ^{37}Cl + 1 ^{34}S + 2 ^{18}O), 201.0, 167.0, 116.2.

Anal. Calcd. for $C_{10}H_6ClNO_2S$: C, 50.11; H, 2.52; N, 5.84. Found: C, 50.11; H, 2.59; N, 5.69.

(*Z*)-5-(4-Chlorobenzylidene)-2-thioxo-thiazolidine-4-one (**5**).

This compound was obtained according to the above general procedure for Knoevenagel condensation reaction as a pale yellow solid; mp 227-230 °C; ^{1}H NMR: δ (ppm) 7.41(m, 2H, ArH), 7.65 (m, 2H, ArH), 7.86 (s, 1H, =CHAr), 13.74 (bs, 1H, NH); MS: m/z (%) found 253.8 (100), calcd 254 $(M-H)^-$. (M-H)+2 (41.38%, 1 ^{37}Cl + 2 ^{34}S + 1 ^{18}O), 119.2, 131.0.

Anal. Calcd. for $C_{10}H_6ClNOS_2$: C, 46.97; H, 2.36; N, 5.48. Found: C, 47.12; H, 2.53; N, 5.31.

(*Z*)-5-(4-Methoxybenzylidene)-thiazolidine-2,4-dione (**6**).

This compound was obtained according to the above general procedure for Knoevenagel condensation reaction as a yellow solid; mp 217-219 °C; ^{1}H NMR: δ (ppm) 3.81(s, 3H, OCH_3), 7.09 (m, 2H, ArH), 7.56 (m, 2H, ArH), 7.75 (s, 1H, =CHAr), 12.49 (bs, 1H, NH); MS: m/z (%) found 234.0 (100), calcd 234 $(M-H)^-$. 163.0, 120.0, 116.2.

Anal. Calcd. for $C_{11}H_9NO_3S$: C, 56.16; H, 3.86; N, 5.95. Found: C, 55.91; H, 4.06; N, 5.89.

(*Z*)-5-(4-Methoxybenzylidene)-2-thioxo-thiazolidine-4-one (**7**).

This compound was obtained according to the above general procedure for Knoevenagel condensation reaction as yellow crystals; mp 233-235 °C; ^{1}H NMR: δ (ppm) 3.82 (s, 3H, OCH_3), 7.10 (m, 2H, ArH), 7.56 (m, 2H, ArH), 7.62 (s, 1H, =CHAr), 13.72 (bs, 1H, NH); MS: m/z (%) found 250.0 (100), calcd 250 $(M-H)^-$. 105.0, 131.0, 92.0.

Anal. Calcd. for $C_{11}H_9NO_2S_2$: C, 52.57; H, 3.61; N, 5.57. Found: C, 52.59; H, 3.74; N, 5.35.

(*Z*)-5-(4-Hydroxybenzylidene)-thiazolidine-2,4-dione (**8**).

This compound was obtained according to the above general procedure for Knoevenagel condensation reaction as a yellow solid; mp >300 °C; ^{1}H NMR: δ (ppm) 6.92 (m, 2H, ArH), 7.40 (m, 2H, ArH), 7.68 (s, 1H, =CHAr), 10.28 (s, 1H, ArOH), 12.42 (bs, 1H, NH); MS: m/z (%) found 220.2 (100), calcd 220 $(M-H)^-$. 148.2, 120.1.

Anal. Calcd. for $C_{10}H_7NO_3S$: C, 54.29; H, 3.19; N, 6.33. Found: C, 54.10; H, 3.30; N, 6.29.

(*Z*)-5-(4-Hydroxybenzylidene)-2-thioxo-thiazolidine-4-one (**9**).

This compound was obtained according to the above general procedure for Knoevenagel condensation reaction as a pink solid; mp 287-290 °C; ^{1}H NMR: δ (ppm) 6.92 (m, 2H, ArH), 7.42 (m, 2H, ArH), 7.58 (s, 1H, =CHAr), 10.44 (s, 1H, ArOH), 13.7 (bs, 1H, NH); MS: m/z (%) found 235.8 (100), calcd 236 $(M-H)^-$. 176.6, 131.0.

Anal. Calcd. for $C_{10}H_7NO_2S_2$: C, 50.62; H, 2.97; N, 5.90. Found: C, 50.45; H, 2.69; N, 5.72.

(*Z*)-5-(4-Benzyloxy-3-methoxybenzylidene)-thiazolidine-2,4-dione (**10**).

This compound was obtained according to the above general procedure for Knoevenagel condensation reaction as a pale yellow solid; mp 221-223 °C; ^{1}H NMR: δ (ppm) 3.84 (s, 3H, OCH_3), 5.15 (s, 2H, OCH_2), 7.14-7.23 (m, 3H, ArH), 7.36 (m, 5H, ArH), 7.75 (s, 1H, =CHAr), 12.51 (bs, 1H, NH); MS: m/z (%) found 340.0 (100), calcd 340 $(M-H)^-$.325.1, 289.0, 248.8, 116.2, 91.0, 76.5.

Anal. Calcd. for $C_{18}H_{15}NO_4S$: C, 63.33; H, 4.43; N, 4.10. Found: C, 63.48; H, 4.40; N, 4.23.

(*Z*)-5-(4-Benzyloxy-3-methoxybenzylidene)-2-thioxo-thiazolidine-4-one (**11**).

This compound was obtained according to the above general procedure for Knoevenagel condensation reaction as a pink solid; mp 216-219 °C; ^{1}H NMR: δ (ppm) 3.84 (s, 3H, OCH_3), 5.15 (s, 2H, OCH_2), 7.16-7.24 (m, 3H, ArH), 7.36 (m, 5H, ArH), 7.71 (s, 1H, =CHAr), 13.86 (bs, 1H, NH); MS: m/z (%) found 356.01 (100), calcd 356 $(M-H)^-$. 272.0, 162.1, 91.0, 76.5.

Anal. Calcd. for $C_{18}H_{15}NO_3S_2$: C, 60.48; H, 4.23; N, 3.92. Found: C, 60.58; H, 4.15; N, 3.79.

(*Z*)-5-(3-Hydroxybenzylidene)-thiazolidine-2,4-dione (**12**).

This compound was obtained according to the above general procedure for Knoevenagel condensation reaction as a cream solid; mp 291-294 °C; ^{1}H NMR: δ (ppm) 6.8-7.1 (m, 3H, ArH), 7.3 (m, 1H, ArH), 7.72 (s, 1H, =CHAr), 9.96 (s, 1H, ArOH), 12.62 (bs, 1H, NH); MS: m/z (%) found 220.0, calcd 220 $(M-H)^-$ .149.2 (100), 116.2

Anal. Calcd. for $C_{10}H_7NO_3S$: C, 54.29; H, 3.19; N, 6.33. Found: C, 54.10; H, 3.30; N, 6.29.

(*Z*)-5-(3-Hydroxybenzylidene)-2-thioxo-thiazolidine-4-one (**13**).

This compound was obtained according to the above general procedure for Knoevenagel condensation reaction as a yellow solid; mp 258-261°C; ^{1}H NMR: δ (ppm) 6.94 (m, 3H, ArH), 7.34 (m, 1H, ArH), 7.73 (s, 1H, =CHAr), 9.98 (s, 1H, ArOH), 13.82 (bs, 1H, NH); MS: m/z (%) found 237.8, calcd 238 $(M+H)^+$. 205.0, 149.2, 131.0 (100).

Anal. Calcd. for $C_{10}H_7NO_2S_2$: C, 50.62; H, 2.97; N, 5.90. Found: C, 50.51; H, 2.75; N, 5.89.

(*Z*)-5-Benzylidene-thiazolidine-2,4-dione (**14**).

This compound was obtained according to the above general procedure for Knoevenagel condensation reaction as a pale yellow crystals; mp 248-250 °C; ^{1}H NMR: δ (ppm) 7.47 - 7.59 (m, 5H, ArH), 7.79(s, 1H, =CHAr), 12.62 (bs, 1H, NH); MS: m/z (%) found 204.0 (100), calcd 204 $(M-H)^-$. 132.4, 116.2, 41.4.

Anal. Calcd. for $C_{10}H_7NO_2S$: C, 58.52; H, 3.44; N, 6.82. Found: C, 58.69; H, 3.51; N, 6.77.

(*Z*)-5-Benzylidene-2-thioxo-thiazolidine-4-one (**15**).

This compound was obtained according to the above general procedure for Knoevenagel condensation reaction as a yellow

crystals; mp 209-211 °C; ^{1}H NMR: δ(ppm) 7.55 (m, 5H, ArH), 7.68 (s, 1H, =CHAr), 13.89 (bs, 1H, NH); MS: m/z (%) found 220.0 (100), calcd 220 (M-H)$^-$. 205.0, 177.0, 131.0, 41.4.

Anal. Calcd. for $C_{10}H_7NOS_2$: C, 54.28; H, 3.19; N, 6.33. Found: C, 54.03; H, 3.27; N, 6.29.

(Z)-5-(1H-Imidazol-4 yl methylene)-thiazolidine-2,4-dione (**16**).

This compound was obtained according to the above general procedure for Knoevenagel condensation reaction as a pale yellow solid; mp 240-242 °C; ^{1}H NMR: δ (ppm) 7.72 (s, 1H, ArH), 7.84 (s, 1H, ArH), 7.54 (s, 1H, =CHAr), 12.66 (bs, 1H, NH), 11.38 (bs, 1H, NH (imidazole)); MS: m/z (%) found 194.0 (100), calcd 194 (M-H)$^-$. 151.0, 116.0.

Anal. Calcd. for $C_7H_5N_3O_2S$: C, 43.07; H, 2.58; N, 21.53. Found: C, 42.93; H, 2.64; N, 21.50.

(*Z*)-5-(1H-Imidazol-4 yl methylene)-2-thioxo-thiazolidine-4-one (**17**).

This compound was obtained according to the above general procedure for Knoevenagel condensation reaction as a yellow solid; mp 215-217 °C; ^{1}H NMR: δ (ppm) 7.70 (s, 1H, ArH), 7.83 (s, 1H, ArH), 7.52 (s, 1H, =CHAr), 13.79 (bs, 1H, NH), 11.27 (bs, 1H, NH (imidazole)); MS: m/z (%) found 210.0 (100), calcd 210 (M-H)$^-$. 151.0, 131.0.

Anal. Calcd. for $C_7H_5N_3OS_2$: C, 39.80; H, 2.39; N, 19.89. Found: C, 39.49; H, 2.45; N, 19.82.

(Z)-5-(4-Hydroxy-3-methoxybenzylidene)-thiazolidine-2,4-dione (**18**).

This compound was obtained according to the above general procedure for Knoevenagel condensation reaction as a yellow solid; mp 224-226 °C; ^{1}H NMR: δ (ppm) 3.84 (s, 3H, OCH_3), 6.94 (m, 1H, ArH), 7.08 (m, 1H, ArH), 7.20 (s, 1H, ArH) 7.84 (s, 1H, ArH), 7.68 (s, 1H, =CHAr), 12.50 (bs, 1H, NH); MS: m/z (%) found 250.0 (100), calcd 250 (M-H)$^-$.179.0, 116.2.

Anal. Calcd. for $C_{11}H_9NO_4S$: C, 52.58; H, 3.61; N, 5.57. Found: C, 52.60; H, 3.57; N, 5.54.

(*Z*)-5-(4-Hydroxy-3-methoxybenzylidene)-2-thioxo-thiazolidine-4-one (**19**).

This compound was obtained according to the above general procedure for Knoevenagel condensation reaction as a yellow solid; mp 238-240 °C; ^{1}H NMR: δ (ppm) 3.84 (s, 3H, OCH_3), 6.94 (m, 1H, ArH), 7.08 (m, 1H, ArH), 7.20 (s, 1H, ArH) 7.84 (s, 1H, ArH), 7.68 (s, 1H, =CHAr), 12.50 (bs, 1H, NH); MS: m/z (%) found 266.0(100), calcd 266 (M-H)$^-$. 194.0, 131.0.

Anal. Calcd. for $C_{11}H_9NO_3S_2$: C, 49.42; H, 3.39; N, 5.24. Found: C, 49.53; H, 3.35; N, 5.03.

(Z)-5-(4-Iopropylbenzylidene)-thiazolidine-2,4-dione (**20**).

This compound was obtained according to the above general procedure for Knoevenagel condensation reaction as white crystals; mp 188-190 °C; ^{1}H NMR: δ (ppm) 1.12 (m, 6H, $(CH_3)_2$), 2.86 (m, 1H, -CH), 7.28 (m, 2H, ArH), 7.38 (m, 1H, ArH), 7.67 (s, 1H, =CHAr), 12.62 (bs, 1H, NH); MS: m/z (%) found 246.0 (100), calcd 246 (M-H)$^-$. 118.2, 116.2.

Anal. Calcd. for $C_{13}H_{13}NO_2S$: C, 63.14; H, 5.30; N, 5.66. Found: C, 63.29; H, 5.22; N, 5.51.

(Z)-5-(4-Isopropylbenzylidene)-2-thioxo-thiazolidine-4-one (**21**).

This compound was obtained according to the above general procedure for Knoevenagel condensation reaction as a white crystals; mp 215-217 °C; ^{1}H NMR: δ (ppm) 1.13 (m, 6H, $(CH_3)_2$), 2.88 (m, 1H, -CH), 7.27 (m, 2H, ArH), 7.37 (m, 1H, ArH), 7.49 (s, 1H, =CHAr), 13.79 (bs, 1H, NH); MS: m/z (%) found 262.0 (100), calcd 262 (M-H)$^-$. 118.2, 131.0.

Anal. Calcd. for $C_{13}H_{13}NOS_2$: C, 59.28; H, 4.98; N, 5.32. Found: C, 59.40; H, 4.89; N, 5.19.

(*Z*)-5-(1H-Indol-5 yl methylene)-thiazolidine-2,4-dione (**22**).

This compound was obtained according to the above general procedure for Knoevenagel condensation reaction as a pink solid; mp 281-283 °C; ^{1}H NMR: δ (ppm) 6.58 (m, 1H, ArH), 7.28 (m, 1H, ArH), 7.48 (m, 2H, ArH) 7.81 (s, 1H, =CHAr), 7.77 (m, 1H, ArH), 12.48 (bs, 1H, NH), 11.5 (bs, 1H, NH(indole)); MS: m/z (%) found 243.2 (100), calcd 243 (M-H)$^-$. 172.0, 144.2, 116.2.

Anal. Calcd. for $C_{12}H_8N_2O_2S$: C, 59.01; H, 3.30; N, 11.47. Found: C, 59.22; H, 3.15; N, 11.42.

(*Z*)-5-(1*H*-Indol-5-yl-methylene)-2-thioxo-thiazolidine-4-one (**23**).

This compound was obtained according to the above general procedure for Knoevenagel condensation reaction as a orange solid; mp 272-275 °C; ^{1}H NMR: δ (ppm) 6.58 (m, 1H, ArH), 7.28 (m, 1H, ArH), 7.48 (m, 2H, ArH) 7.81 (s, 1H, =CHAr), 7.77 (m, 1H, ArH), 13.81 (bs, 1H, NH), 11.52 (bs, 1H, NH(indole)); MS: m/z (%) found 258.8 (100), calcd 259 (M-H)$^-$. 144.2, 131.0.

Anal. Calcd. for $C_{12}H_8N_2OS_2$: C, 55.36; H, 3.10; N, 10.76. Found: C, 55.49; H, 3.24; N, 10.62.

(*Z*)-5-(1-Pyridyl-3-chloro-5-triflurometh yl-2-ylmethylene)-thiazolidine-2,4-dione (**24**).

This compound was obtained according to the above general procedure for Knoevenagel condensation reaction as a brownish black solid; mp 224-226 °C; ^{1}H NMR: δ (ppm) 7.56 (s, 1H, =CH(pyridine)), 8.10 (s, 1H, H-pyridine), 9.11 (s, 1H, H-pyridine), 13.78 (bs, 1H, NH); MS: m/z (%) found 307.0 (100), calcd 307 (M-H)$^-$. (M-H)+2 (37.28%, 1 ^{37}Cl + 1 ^{34}S + 2 ^{18}O), 210.0, 116.2.

Anal. Calcd. for $C_{10}H_4ClF_3N_2O_2S$: C, 38.91; H, 1.31; N, 9.08. Found: C, 38.57; H, 1.57; N, 9.11.

(Z)-5-(1-Pyridyl-3-chloro-5-triflurometh yl-2-ylmethylene)-2-thioxo-thiazolidine-4-one (**25**).

This compound was obtained according to the above general procedure for Knoevenagel condensation reaction as a black solid; mp 233-235 °C; ^{1}H NMR: δ (ppm) 7.56 (s, 1H, = CH(pyridine)), 8.10 (s, 1H, H-pyridine), 9.11 (s, 1H, H-pyridine), 13.78 (bs, 1H, NH); MS: m/z (%) found 323.0 (100), calcd 323 (M-H)$^-$. (M-H)+2 (41.51%, 1 ^{37}Cl + 2 ^{34}S + 1 ^{18}O), 270.0, 210.0, 157.0.

Anal. Calcd. for $C_{10}H_4ClF_3N_2OS_2$: C, 36.99; H, 1.24; N, 8.63. Found: C, 36.68; H, 1.53; N, 8.69.

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