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Ultrasound-assisted green synthesis of 2,4-thiazolidinedione and diaryl substituted pyrazolylthiazolidinediones catalyzed by β -alanine

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Abstract

A new method was carried out for the synthesis of 2,4-thiazolidinedione 3 by heating thiourea and chloroacetyl chloride in water under ultrasonic irradiation. Moreover, a rapid and green method has been developed for the synthesis of a series of diaryl substituted pyrazolyl-2,4-thiazolidinediones 8a-g through the reaction of appropriate pyrazolecarboxaldehydes 7a-g with 2,4-thiazolidinedione 3 using β -alanine as a catalyst. All compounds were characterized by their reported melting points, FT-IR, ^1H and ^{13}C NMR spectroscopy in addition to elemental analysis. This new synthetic method has advantages of being gives a product with high purity, good yield, and short reaction times when compared to the previously reported methods.

Keywords: thiazolidinedione, ultrasonic, knoevenagel, Vilsmeier-haack, pyrazolecarboxaldehydes, β -alanine

1. Introduction

Pyrazole skeleton, a privileged medicinal scaffold, is a remarkable structural motif in the synthesis of an impressive number of biologically active molecules. Their diverse biological activities mainly includes anti-inflammatory, antifungal, antimicrobial, anticancer, anti-tubercular, antiviral, neuroprotective, estrogen receptor ligand, angiotensin-converting enzyme (ACE) inhibitors, anticonvulsant, analgesic, antidiabetic, anti-anxiety, and herbicidal [1, 2]. Nowadays, pyrazole derivatives have attracted great attention since several commercially available drugs have been developed from pyrazole derivatives belonging to different categories with diverse therapeutic activities [1-4] such as celecoxib 1 (COX-2 inhibitor), difenamizole 2 (anti-inflammatory), Lonazolc 3 (anti-inflammatory), pyrazofurin 4 (anti-cancer), rimonabant 5 (anti-obesity), fomepizole 6 (alcohol dehydrogenase inhibitor), deracoxib 7 (NSAID), and sildenafil 8 (phosphodiesterase-5 inhibitor) (Figure 1) [1-4].

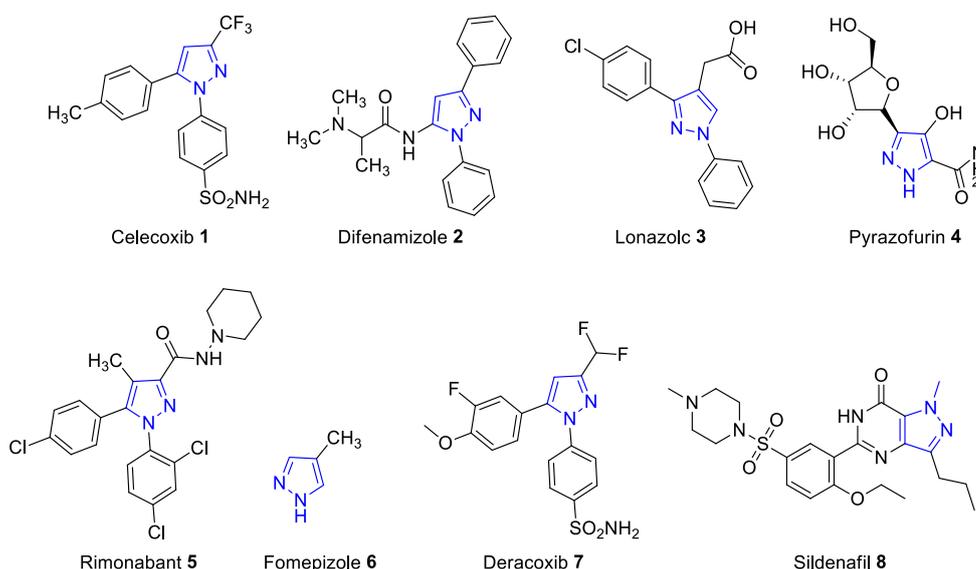


Fig 1: Representative examples of clinically used molecules having pyrazole framework

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On the other hand, 2,4-thiazolidinediones (TZDs), known as glitazones, represent one of the privileged and attractive scaffolds because of its prestigious position in medicinal chemistry, drug design, and drug discovery. Numerous compounds containing the TZD scaffold demonstrates various biological activities, including antihyperglycemic, anticancer, bactericidal, selective PI3 kinase inhibitor fungicidal, antidiarrheal, pesticidal, insecticidal, anti-HIV, antiarthritic, antihistaminic, anti-inflammatory, 15-hydroxyprostaglandin dehydrogenase inhibitors,

antimicrobial, anti-convulsant, anti-ischemic, and tuberculostatic agents [5-10]. Among these, the anti-diabetic activity is the widely studied effect of TZD derivatives and the position of these molecules seems to be most significant as they constitute a subset of commercially employed insulin-sensitizing and non-insulin-dependent diabetes mellitus agents such as pioglitazone 9, ciglitazone 10, rosiglitazone 11, epalrestat 12 and lobeglitazone 13 [11-14] (Figure 2).

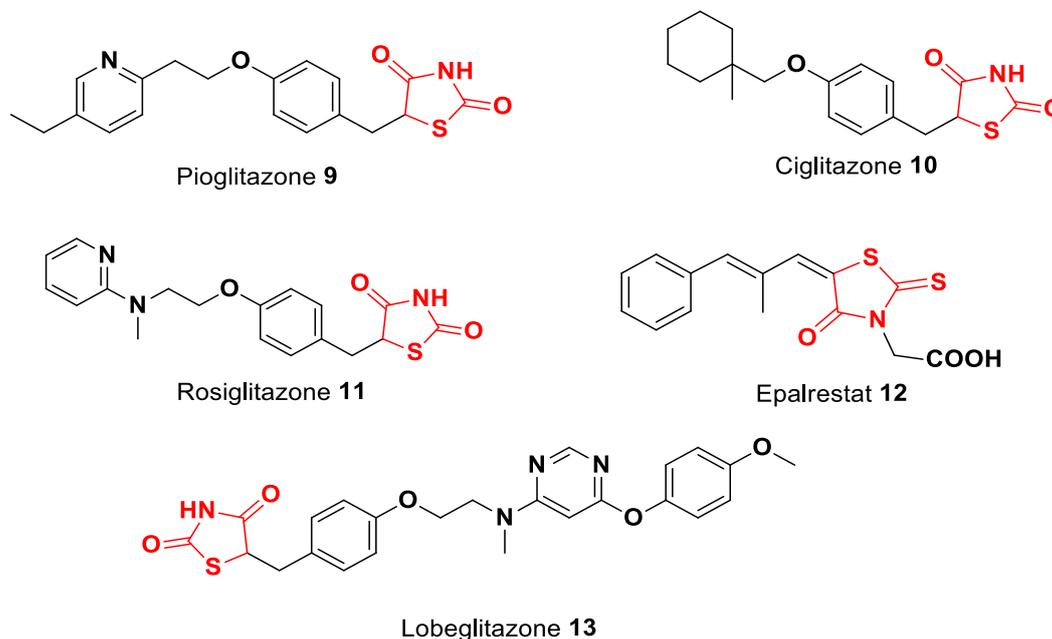


Fig 2: Clinically used molecules having 5-arylidene-2,4-thiazolidinedione derivatives

Obviously, hybridization of 2,4-thiazolidinedione with pyrazole provided new candidates with promising potent biological activities (Figure 3) such as antidiabetic 14 and 15 [15], anticancer 16 [16], antibacterial 17 [9], antifungal 18 [9],

antiviral, antiparasitic, anti-inflammatory activities and VHR protein tyrosine phosphatase inhibitors 19 [17]. Thus, the pyrazole-TZDs allowed to identify several promising drug-like compounds.

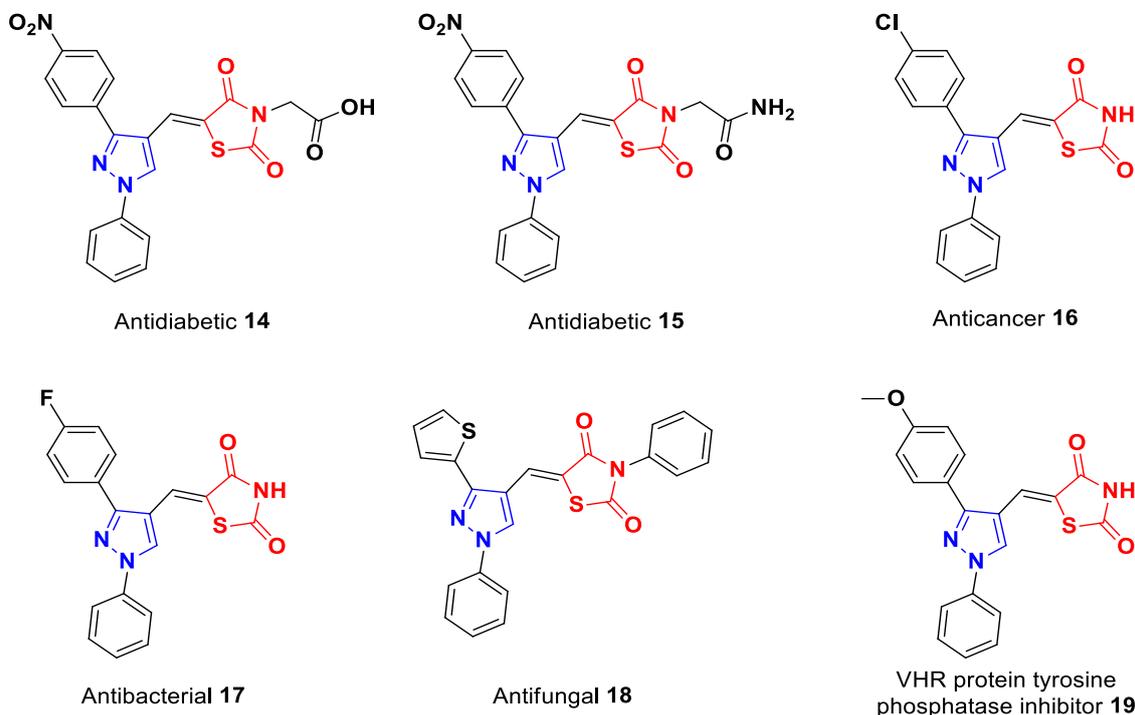


Fig 3: Representative example of biologically active pyrazole-2,4-thiazolidinedione derivatives

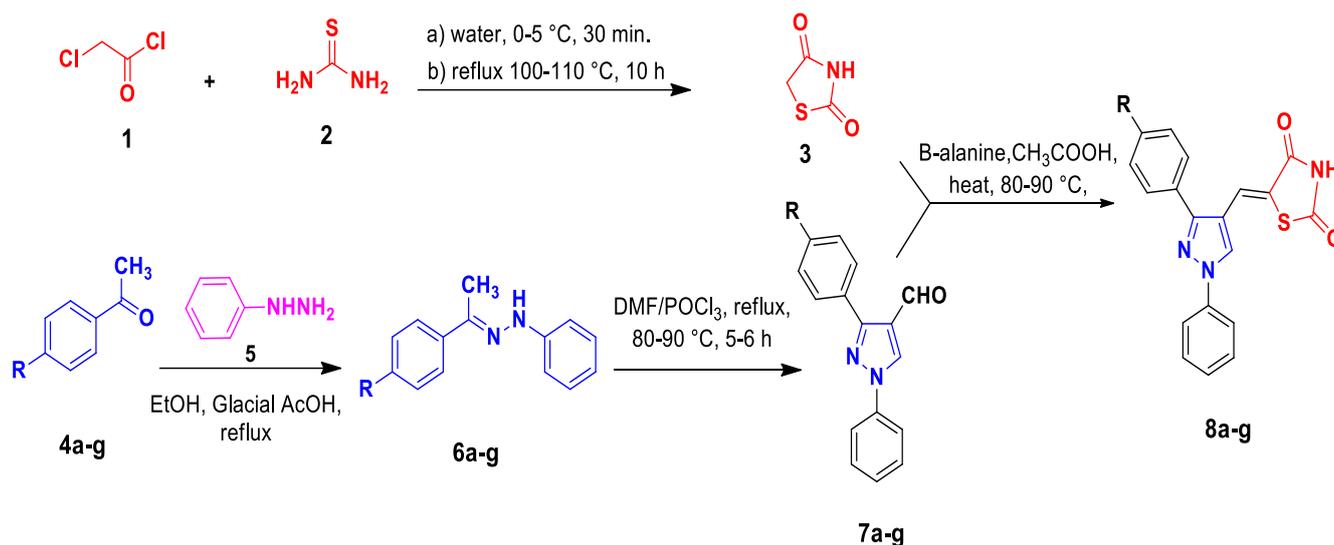
Several methods have been developed for the well-known condensation reaction of the active methylene of TZD with aldehydes or ketones as this is a pivotal step in the synthesis of the above clinically used drugs (Figure 1) [18], therefore, this condensation is of significant commercial value. To achieve this Knoevenagel condensation, several synthetic protocols are reported using several catalysts such as anhydrous sodium acetate, amines, amine derivatives, amine salts, KF-Al₂O₃, glycine, and ionic liquids. Several efforts have also been made to develop an eco-friendly reaction condition for Knoevenagel condensation using L-tyrosine, baker's yeast, or β-alanine [18]. Moreover, condensation of TZD with ketones has been achieved in the presence of piperidinium acetate or ammonium acetate in ethyl acetate or toluene [18, 19]. Several of these existing synthetic protocols for achieving this Knoevenagel condensation step have some drawbacks such as long reaction times, low

yields and leaving toxic residues on aqueous work-up; amine use is also now found to be carcinogenic [20, 21]. Therefore, a facile efficient process is still desirable. The ultrasound technique is extensively used in organic synthesis as it saves time and is a green and eco-friendly method [22-24].

Therefore, encouraged by the above-mentioned facts, the purpose of this work is to adopt an efficient new simple eco-friendly method for the synthesis of TZD in water. In addition, our endeavor is to synthesize a series of diaryl substituted pyrazolyl-TZDs using β-alanine as a catalyst under ultrasonic irradiation.

2. Results and Discussion

The synthetic route for the preparation of the target diaryl substituted pyrazolyl-TZDs 8a-g has been outlined in Scheme 1.

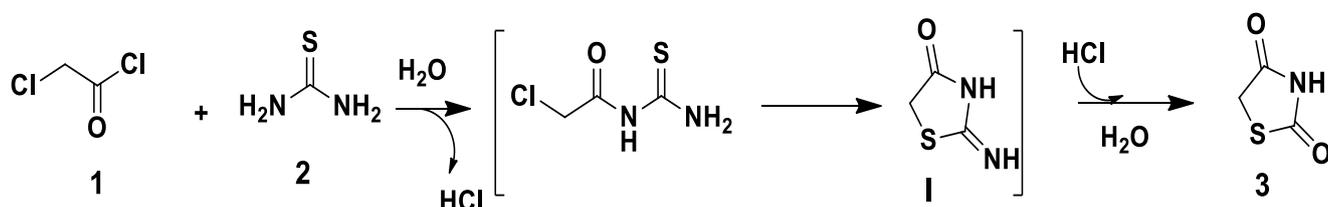


4a, 6a, 7a, 8a: R = H; 4b, 6a, 7b, 8b: R = CH₃; 4c, 6c, 7c, 8c: R = -OCH₃; 4d, 6d, 7d, 8d: R = Br; 4e, 6e, 7e, 8e: R = Cl; 4f, 6f, 7f, 8f: R = F; 4g, 6g, 7g, 8g: R = NO₂

Scheme 1: Synthesis of target diaryl substituted pyrazolyl-TZDs

Initially, we attempted to prepare TZD 3 *via* the conventional reaction of thiourea and chloroacetic acid in water under refluxing conditions [25-27]. However, the reaction required longer times (>10 h) leading to poor chemical yields. Therefore, herein, we tried to carry out the reaction using a novel procedure including the use of thiourea and chloroacetylchloride in water under refluxing conditions (Method A) and under ultrasound irradiation (Method B) as a new method (Table 1). Upon carrying out the reaction under refluxing condition, we noticed that there

are no significant advantages on comparing the reaction time and the yield with the conventional method except avoiding the use of the toxic chloroacetic acid. Additionally, there is no need to externally add HCl, as the *in situ* produced HCl in this method consumed during the reaction in the hydrolysis of the non-isolated 2-imino-thiazolidine-4-one I to get the target TZD 3 as depicted in Scheme 2. Notably, shifting to the ultrasonic irradiation procedure, the reaction time was significantly reduced from 10-12 h to 4-5 h and the yield was slightly improved from 85% up to 90%.



Scheme 2: Proposed mechanism for the synthesis of 2,4-thiazolidinedione (TZD) using chloroacetylchloride in water.

Moreover, Phenylhydrazine derivatives 6a-g were synthesized by treating the appropriate substituted acetophenones 4a-g with phenylhydrazine 5 followed by Vilsmeier-Haack reaction in the presence of DMF and POCl₃ to give pyrazolecarboxaldehydes 7a-g [25-27].

Further, to prepare the target diaryl substituted pyrazolyl-TZDs 8a-g, our initial pilot experiments have been achieved by using the conventional Knoevenagel condensation reaction between the synthesized pyrazolecarboxaldehydes and TZD to yield TZD clubbed pyrazole adducts 8a-g, however, the reaction required longer times (>10 h) leading to poor chemical yields and several byproducts. Then, we opted to carry out the reaction using β-alanine in acetic acid under refluxing conditions (Method A) or under ultrasound

irradiation (Method B) as a green and eco-friendly method (Table 1).

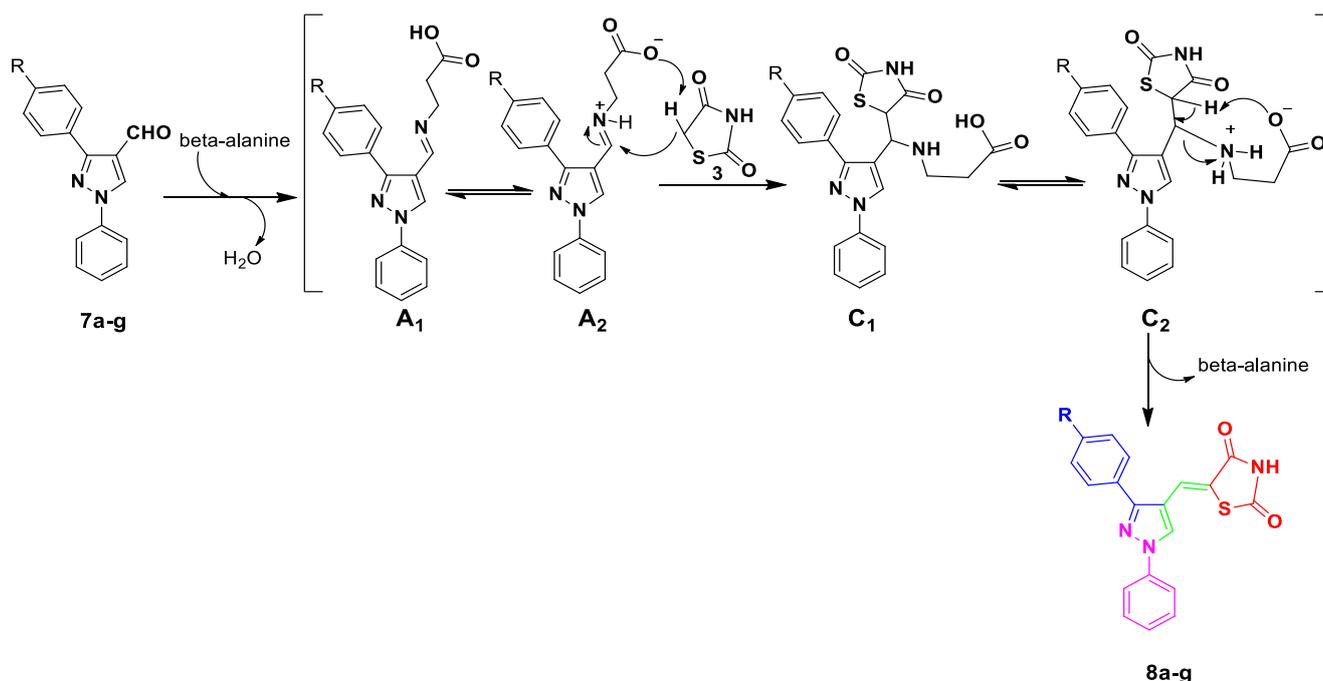
Without β-alanine, at room temperature or at 50 °C, no or inferior chemical yields were obtained even after prolonged reaction time (24 h), respectively, while a considerable yield was obtained (70-84%) upon using β-alanine in acetic acid under refluxing conditions for 60-90 min (Table 1). Notably, after short optimization of the reaction conditions, the best results were obtained when the reaction was catalyzed by β-alanine in acetic acid under ultrasound irradiations at 50 °C for 30-60 min (Table 1). Using these optimized reaction conditions, a variety of diaryl substituted pyrazolyl-TZDs were efficiently obtained in yields of up to 95% and the obtained results are summarized in Table 1.

Table 1: Reaction conditions and yields for synthesis of the synthesized compounds.

| Entry | Cpd | R | Yield (%) / Time (min) | Yield (%) / Time (min) |
|-------|-----|------------------|------------------------|------------------------|
| | | | Method A | Method B |
| 1 | 8a | H | 70/80 | 79/50 |
| 2 | 8b | CH ₃ | 78/90 | 88/60 |
| 3 | 8c | OCH ₃ | 84/90 | 91/60 |
| 4 | 8d | Br | 75/70 | 90/30 |
| 5 | 8e | Cl | 79/70 | 87/30 |
| 6 | 8f | F | 82/50 | 92/25 |
| 7 | 8g | NO ₂ | 72/60 | 95/30 |

A plausible mechanism for this reaction has been suggested in Scheme 3 [28]. The reaction of β-alanine with pyrazolecarboxaldehydes 7a-g leads to the formation imine. Subsequent reaction between the carboxylate anion of the formed imine A₁ and TZD 3 gives rise to TZD anion.

Meanwhile, aldehyde can form iminium ion A₂. The iminium ion A₂ condenses with TZD anion to form intermediate C₁ and C₂, which could be converted to diaryl substituted pyrazolyl-TZDs 8a-g after elimination of β-alanine.



Scheme 3: Plausible mechanism for Knoevenagel reaction catalyzed by β-alanine.

The mechanism supports our observation that aldehydes having electron-donating groups required somewhat longer reaction times that is attributed to the slower formation of intermediate imine (Table 1, entries 1 and 2). On the other hand, aldehydes bearing electron-withdrawing groups reacted faster owing to the rapid formation of imine (entries 4-6). Overall, the reaction worked well with a variety of

aldehydes including those bearing an electron-withdrawing group and electron-donating group and the corresponding products were obtained with high yields in shorter reaction times.

Of important mentioning that these compounds have previously reported [25-27]. The spectral data (IR, ¹H NMR and ¹³C NMR of the compounds reported in literature match

with the spectral data of our products. However, melting points of our products were found to be different from melting points of products synthesized by Youssef *et al.*,^[26] and Sridhar *et al.*,^[27] while it is consistency with melting points reported by Prakash *et al.*,^[25]. Therefore, it became important to synthesize authentic sample of 8c as

representative example using the reported conditions. Since, TLC and spectral data of the compound 8c (Figure 4a-c) prepared by the known procedures^[25-27] were identical to those obtained by our conditions, the reported melting points might be in error with Youssef *et al.*,^[26] and Sridhar *et al.*,^[27] while it is in agreement with Prakash *et al.*,^[25].

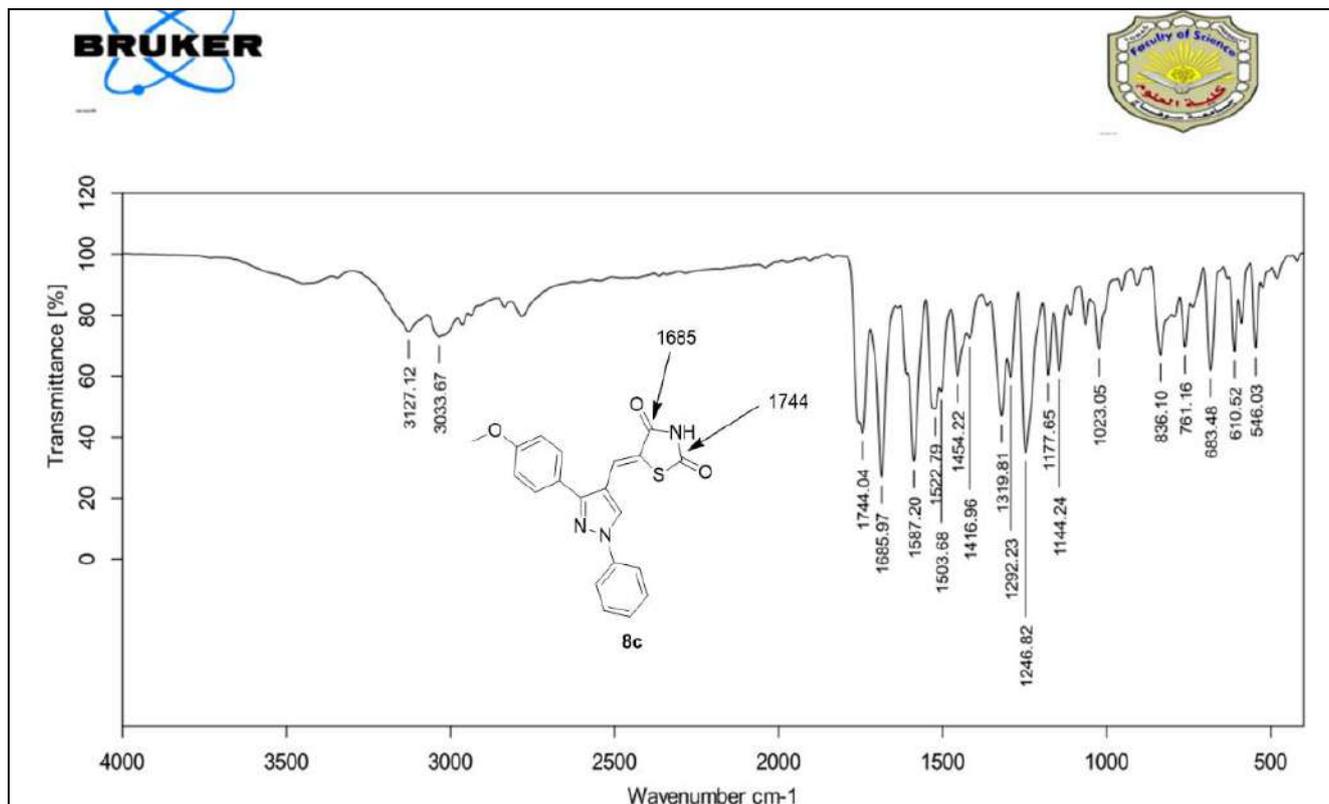


Fig 4a: Characteristics value of IR of compound 8c.

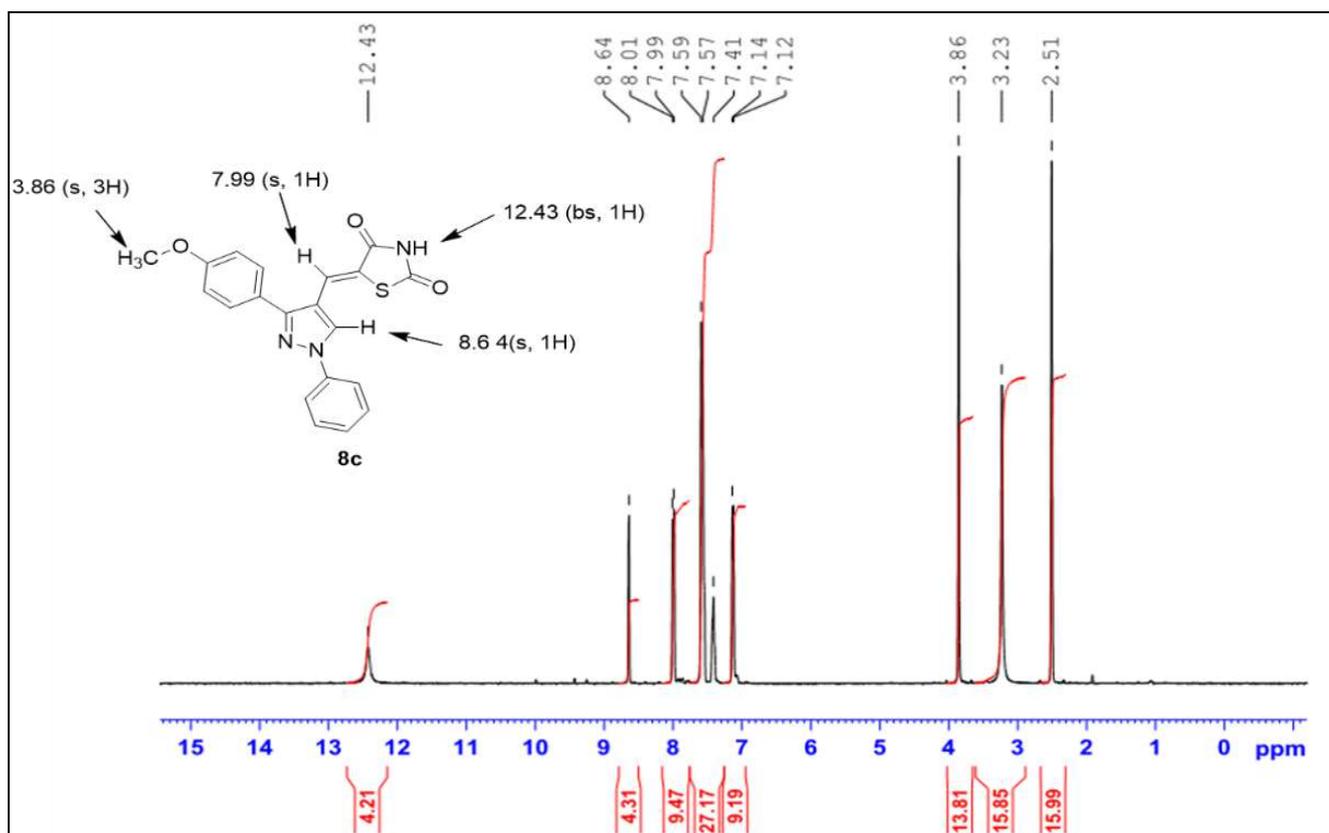


Fig 4b: Characteristics value of ¹H NMR of compound 8c.

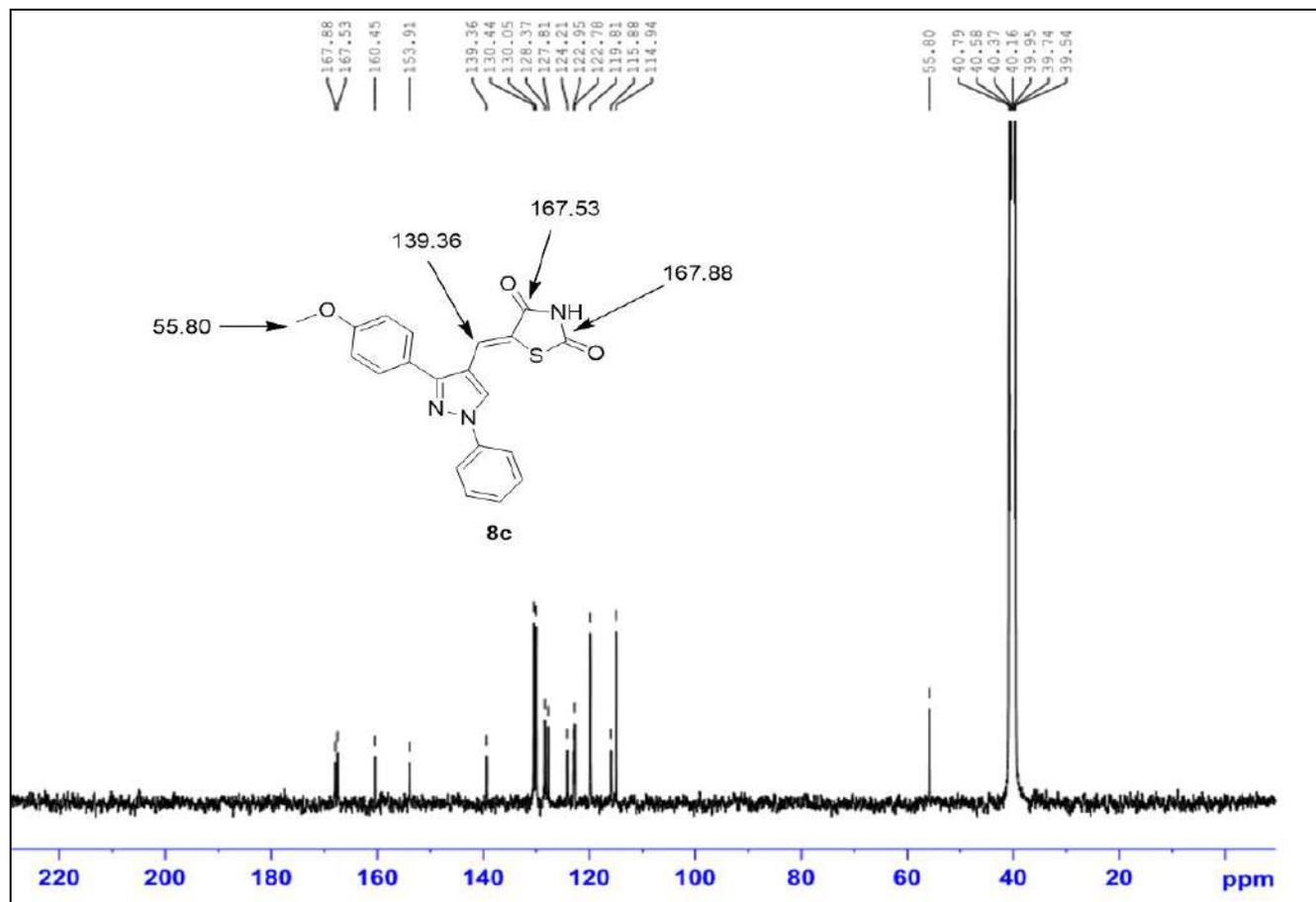


Fig 4c: Characteristics value of ^{13}C NMR and IR of compound **8c**.

3. Conclusion

In summary, an eco-friendly synthesis of TZD **3** was carried out by heating thiourea and chloroacetyl chloride in water under ultrasonic irradiation. Moreover, a protocol has been developed to carry out the Knoevenagel condensation reaction with TZD and pyrazolecarboxaldehydes using β -alanine as a catalyst to produce pyrazolyl-TZDs (**8a-g**). Compared to the established methods, the new synthetic method and the new reaction conditions has several advantages, such as allowing significant reduction in the formation of byproducts, good yield, simple work-up, and short reaction times. Future studies in our group will focus on exploring the application scope of this method using wide scope of substrates.

4. Experimental

4.1 Synthesis of 2,4-thiazolidinedione **3**

4.1.1 Conventional method

Equimolar amounts of thiourea (0.6 M) and chloroacetic acid (0.6 M) were dissolved each in 60 mL of water separately and mixed slowly at 0-5 °C and stirred for 20 min to form a white precipitate of 2-imino-thiazolidine-4-one. Conc. HCl (60 mL) was added and refluxed for about 10-12 h. Reaction was monitored through TLC (Chloroform:Methanol, 9:1). Reaction mixture was allowed to cool to form white solid crystals, washed with water, and dried. White crystals, yield 79%, m.p. 123-125 as reported [29, 30].

4.1.2 Method A

To an ice-cold solution of thiourea **2** (7.61 g, 10 mmol) in 10 mL water, was added chloro acetylchloride **1** (12.42 g,

11 mmol) drop-wise over a period of 20 min and stirring was continued for 15 min at rt to obtain white precipitates. Then, the reaction mixture was refluxed for 8–10 h at 100–110 °C with stirring. On cooling, white needles of TZD **3** were solidified which were filtered, washed with water, dried and recrystallized from ethanol. White crystals, yield: 85%; m.p. 123-125 °C; as reported [29, 30].

4.1.3 Method B

In a round-bottomed flask, to thiourea **2** (7.61 g, 10 mmol) in 10 mL water, chloroacetylchloride **1** (12.42 g, 11 mmol) was added drop-wise over a period of 20 min at 0-5 °C, and stirring was continued for 15 min at rt to obtain white precipitates. Then, the reaction mixture was placed in an ultrasonic bath at 50 °C for 4 h. After completion of the reaction, as monitored by TLC, and on cooling, white needles of TZD **3** were solidified which were filtered, washed with water, dried, and recrystallized from ethanol. White crystals, yield: 95%; m.p. 123-125 °C; as reported [29, 30].

4.2 General procedure for synthesis of 5-[(3-Aryl-1-phenyl-1H-pyrazol-4-yl)methylene]-2,4-thiazolidinediones (**8a-f**)

4.2.1 Method A

To a mixture of 1,3-thiazolidine-2,4-dione **3** (0.8 g, 4 mmol) and the appropriate 3-(substituted phenyl)-1-phenyl-1H-pyrazole-4-carboxaldehydes **7a-f** (4 mmol) in glacial acetic acid (10 mL), β -alanine (0.71 g, 8 mmol) was added and the reaction mixture was heated under reflux at 80–90 °C for 60-90 min. After completion of the reaction, as monitored by TLC, a small portion of water was added, and the

precipitated solids was filtered off, washed with water, dried, and recrystallized from ethanol to give pure compounds 8a-f in 70–84% yield.

4.2.2 Method B

In a round-bottomed flask, a mixture of TZD 3 (0.8 g, 4 mmol) and the appropriate 3-(substituted phenyl)-1-phenyl-1H-pyrazole-4-carbaldehydes 7a-f (4 mmol) in glacial acetic acid (10 mL), β -alanine (0.71 g, 8 mmol) were placed in an ultrasonic bath at 50 °C for 30–90 min. After completion of the reaction, as monitored by TLC, a small portion of water was added, and the precipitated solids was filtered off, washed with water, dried, and recrystallized from ethanol to give pure compounds 8a-f, yield: 79–95%.

4.2.3 (Z)-5-[[1,3-Diphenyl-1H-pyrazol-4-yl]methylene]-2,4-thiazolidinedione (8a)

Yellow solid, m.p.: 290-293 °C (reported m.p.: 292-294 °C);^[25] IR (KBr) ν_{\max} cm⁻¹: 1738 and 1688 (C=O); ¹H NMR (400 MHz, DMSO-*d*₆): δ (ppm) 12.51 (bs, 1H, N-H, exch. D₂O); 8.71 (s, 1H, C₅-H of pyrazole); 8.02-8.00 (d, *J* = 8 Hz, 2H, ArH), 7.79-7.43 (m, 9H, Ar-H and -CH=C-); ¹³C NMR (100 MHz, DMSO-*d*₆): δ (ppm) 168.36 (C₂=O), 167.16 (C₄=O), 153.81 (-C=N-), 139.32 (=CH-), 133.97, 131.58, 130.12, 129.38, 129.12, 128.43, 127.90, 125.89, 121.78, 119.88 and 116.19. Anal. Calcd. For C₁₉H₁₃N₃O₂S: C, 65.69; H, 3.77; N, 12.10. Found: C, 65.72; H, 3.81; N, 12.13%.

4.2.4 (Z)-5-[[1-Phenyl-3-p-tolyl-1H-pyrazol-4-yl]methylene]-2,4-thiazolidinedione (8b)

Light brown solid, m.p.: 290-291 °C (reported m.p. = 288-290 °C)^[25]; IR (KBr) ν_{\max} cm⁻¹: 1738 and 1688 (C=O); ¹H NMR (400 MHz, DMSO-*d*₆): δ (ppm) 12.62-12.51 (bs, 1H, N-H, exch. D₂O); 8.65 (s, 1H, C₅-H of pyrazole); 8.00-7.98 (d, *J* = 7.8 Hz, 2H, Ar-H), 7.61-7.31 (m, 8H, Ar-H and -CH=C-), 2.38 (s, 3H, CH₃); ¹³C NMR (100 MHz, DMSO-*d*₆): δ (ppm) 167.14 (C₂=O), 166.29 (C₄=O), 152.12 (-C=N-), 139.25 (=CH-), 134.21, 131.78, 130.32, 130.13, 129.86, 129.14, 128.87, 124.97, 119.71, 119.36, 115.68 and 21.25. Anal. Calcd. For C₂₀H₁₅N₃O₂S: C, 66.46; H, 4.18; N, 11.63. Found: C, 66.39; H, 4.02; N, 11.71%.

4.2.5 (Z)-5-[[3-(4-Methoxyphenyl)-1-phenyl-1H-pyrazol-4-yl]methylene]-2,4-thiazolidinedione (8c)

Yellow solid, m.p.: 293-294 °C; (reported m.p.: 293-295 °C);^[25] IR (KBr) ν_{\max} cm⁻¹: 1744 and 1685 (C=O); ¹H NMR (400MHz, DMSO-*d*₆): δ (ppm) 12.4 (bs, 1H, N-H, exch. D₂O); 8.64 (s, 1H, C₅-H of pyrazole); 8.01-7.98 (d, 2H, Ar-H, *J* = 7.5 Hz); 7.59-7.55 (m, 5H, Ar-H and =CH); 7.41-7.36 (m, 1H, Ar-H); 7.14-7.12 (d, 2H, Ar-H, *J* = 7.2 Hz); 3.86 (s, 3H, OCH₃); ¹³C NMR (100 MHz, DMSO-*d*₆): δ (ppm) 167.88 (C₂=O), 167.53 (C₄=O), 160.45 (C-OCH₃), 153.91 (-C=N-), 139.36 (=CH-), 130.44, 130.05, 128.37, 127.81, 124.21, 122.95, 122.78, 119.81, 115.88, 114.94 and 55.80. Anal. Calcd. For C₂₀H₁₅N₃O₃S: C, 63.65; H, 4.01; N, 11.13. Found: C, 63.42; H, 3.87; N-11.25%.

4.2.6 (Z)-5-[[3-(4-Bromophenyl)-1-phenyl-1H-pyrazol-4-yl]methylene]-2,4-thiazolidinedione (8d)

Yellow solid, m.p.: 299-301 °C; (reported m.p.: 301-303 °C)^[25] IR (KBr) ν_{\max} cm⁻¹: 1754 and 1686 (C=O); ¹H NMR (400MHz, DMSO-*d*₆): δ (ppm) 12.29-12.25 (bs, 1H, N-H, exch. D₂O); 8.65 (s, 1H, C₅-H of pyrazole); 7.98-7.42 (m,

10 H, Ar-H and -CH=C-); ¹³C NMR (100 MHz, DMSO-*d*₆): δ (ppm): 168.03 (C₂=O), 167.99 (C₄=O), 152.63 (-C=N-), 139.24 (=CH-), 132.38, 131.17, 130.99, 130.05, 128.62, 127.96, 124.18, 122.96, 121.80, 119.87 and 116.17. Anal. Calcd. For C₁₉H₁₂BrN₃O₂S: C, 53.53; H, 2.84; N, 9.86. Found: C, 53.47; H, 2.71; N-9.77%.

4.2.7 (Z)-5-[[3-(4-Chlorophenyl)-1-phenyl-1H-pyrazol-4-yl]methylene]-2,4-thiazolidinedione (8e)

Creamish solid, m.p.: 325-327 °C as reported^[25] IR (KBr) ν_{\max} cm⁻¹: 1739 and 1685 (C=O); ¹H NMR (400 MHz, DMSO-*d*₆): δ (ppm) 12.58-12.44 (bs, 1H, N-H, exch. D₂O); 8.64 (s, 1H, C₅-H of pyrazole); 7.99-7.97(d, *J* = 7.2 Hz, 2H, Ar-H), 7.67-7.41 (m, 8H, Ar-H and =CH); ¹³C NMR (100 MHz, DMSO-*d*₆): δ (ppm) 167.82 (C₂=O), 167.51 (C₄=O), 152.62 (-C=N-), 139.22 (=CH-), 134.37, 130.73, 130.04, 129.45, 128.63, 127.97, 123.74, 122.13, 119.87 and 116.09; Anal. Calcd. For C₁₉H₁₂ClN₃O₂S: C, 59.76; H, 3.17; N, 11.00. Found: C, 59.68; H, 3.04; N, 10.88%.

4.2.8 (Z)-5-[[3-(4-Fluorophenyl)-1-phenyl-1H-pyrazol-4-yl]methylene]-2,4-thiazolidinedione (8f)

Yellow solid, m.p.: 297-299 °C; (reported m.p.: 298-300 °C)^[25]; IR (KBr) ν_{\max} cm⁻¹: 1758 and 1696 (C=O); ¹H NMR (400 MHz, DMSO-*d*₆): δ (ppm) 12.64-12.52 (bs, 1H, N-H, exch. D₂O); 8.69 (s, 1H, C₅-H of pyrazole); 8.02-8.00 (d, *J* = 7.2 Hz, 2H, Ar-H), 7.76-7.43 (m, 8H, Ar-H and =CH); ¹³C NMR (100 MHz, DMSO-*d*₆): δ (ppm) 168.21 (C₂=O), 168.09 (C₄=O), 153.93 (-C=N-), 139.28 (=CH-), 134.84, 131.12, 130.35, 129.54, 128.78, 128.11, 124.03, 122.56, 119.99 and 116.47; Anal. Calcd. For C₁₉H₁₂ClN₃O₂S: C, 62.46; H, 3.31; N, 11.50. Found: C, 62.25; H, 3.47; N, 11.37%.

4.2.9 (Z)-5-[[3-(4-Nitrophenyl)-1-phenyl-1H-pyrazol-4-yl]methylene]-2,4-thiazolidinedione (8g)

Brown solid, m.p.: 299-301 °C as reported^[25] IR (KBr) ν_{\max} cm⁻¹: 1750 and 1709 (C=O); ¹H NMR (400MHz, DMSO-*d*₆): δ (ppm) 12.5 (bs, 1H, N-H, exch. D₂O); 8.75 (s, 1H, C₅-H of pyrazole); 8.42-8.40 (d, *J* = 8.8 Hz, 2H, Ar-H), 8.04-8.02 (d, *J* = 7.6 Hz, 2H, Ar-H), 7.98-7.96 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.62-7.59 (m, 4H, Ar-H and =CH-), 7.47-7.45 (t, *J* = 7.6 Hz, 1H, Ar-H); ¹³C NMR (100 MHz, DMSO-*d*₆): δ (ppm) 167.75 (C₂=O), 167.52 (C₄=O), 151.50 (-C=N-), 148.11 (C-NO₂), 139.17 (=CH-), 138.36, 130.12, 129.17, 128.27, 124.59, 124.43, 121.74, 120.08 and 116.61; Anal. Calcd. For C₁₉H₁₂N₄O₄S: C, 58.16; H, 3.08; N, 14.28. Found: C, 58.04; H, 3.21; N-14.19%.

5. References

1. Ansari A, Ali A, Asif M. Biologically active pyrazole derivatives. *New Journal of Chemistry* 2017;41(1):16-41.
2. Naim MJ, Alam O, Farah Nawaz M, Alam J, Alam P. Current status of pyrazole and its biological activities. *Journal of pharmacy & bioallied sciences* 2016;8(1):2-17.
3. Karrouchi K, Radi S, Ramli Y, Taoufik J, Mabkhot YN, Al-Aizari FA. Synthesis and pharmacological activities of pyrazole derivatives: a review. *Molecules* 2018;23(1):134.
4. Faisal M, Saeed A, Hussain S, Dar P, Larik FA. Recent developments in synthetic chemistry and biological

- activities of pyrazole derivatives. *Journal of Chemical Sciences* 2019;131(8):1-30.
- Clark-Lewis J. 2, 4-Oxazolidinediones. *Chemical reviews* 1958;58(1):63-99.
 - Hughes SJ, Millan DS, Kilty IC, Lewthwaite RA, Mathias JP, O'Reilly MA *et al.* Fragment based discovery of a novel and selective PI3 kinase inhibitor. *Bioorganic & medicinal chemistry letters* 2011;21(21):6586-6590.
 - Abd Alhameed R, Almarhoon Z, Bukhari SI, El-Faham A, de la Torre BG, Albericio F. Synthesis and antimicrobial activity of a new Series of thiazolidine-2, 4-diones carboxamide and amino acid derivatives. *Molecules* 2020;25(1):105.
 - Szychowski KA, Kaminsky DV, Leja ML, Kryshchshyn AP, Lesyk RB, Tobiasz J *et al.* Anticancer properties of 5Z-(4-fluorobenzylidene)-2-(4-hydroxyphenylamino)-thiazol-4-one. *Scientific reports* 2019;9(1):1-16.
 - Naim MJ, Alam MJ, Ahmad S, Nawaz F, Shrivastava N, Sahu M *et al.* Therapeutic journey of 2,4-thiazolidinediones as a versatile scaffold: An insight into structure activity relationship. *European journal of medicinal chemistry* 2017;129:218-250.
 - Rosa F, Osorio JS, Trevisi E, Yanqui-Rivera F, Estill CT, Bionaz M. 2, 4-Thiazolidinedione treatment improves the innate immune response in dairy goats with induced subclinical mastitis. *PPAR research* 2017.
 - Naim MJ, Alam MJ, Nawaz F, Naidu V, Aaghaz S, Sahu M *et al.* Synthesis, molecular docking and anti-diabetic evaluation of 2, 4-thiazolidinedione based amide derivatives. *Bioorganic chemistry* 2017;73:24-36.
 - Yasmin S, Jayaprakash V. Thiazolidinediones and PPAR orchestra as antidiabetic agents: From past to present. *European journal of medicinal chemistry* 2017;126:879-893.
 - Nanjan MJ, Mohammed M, Kumar BRP, Chandrasekar MJN. Thiazolidinediones as antidiabetic agents: a critical review. *Bioorganic chemistry* 2018;77:548-567.
 - Nazreen S, Alam MS, Hamid H, Yar MS, Dhulap A, Alam P *et al.* Design, Synthesis, and Biological Evaluation of Thiazolidine-2, 4-dione Conjugates as PPAR- γ Agonists. *Archiv der Pharmazie* 2015;348(6):421-432.
 - Bansal G, Thanikachalam PV, Maurya RK, Chawla P, Ramamurthy S. An overview on medicinal perspective of thiazolidine-2, 4-dione: A remarkable scaffold in the treatment of type 2 diabetes. *Journal of advanced research* 2020;23:163-205.
 - Sahiba N, Sethiya A, Soni J, Agarwal DK, Agarwal S. Saturated five-membered thiazolidines and their derivatives: from synthesis to biological applications. *Topics in Current Chemistry* 2020;378(2):1-90.
 - Havrylyuk D, Roman O, Lesyk R. Synthetic approaches, structure activity relationship and biological applications for pharmacologically attractive pyrazole/pyrazoline-thiazolidine-based hybrids. *European journal of medicinal chemistry* 2016;113:145-166.
 - Thari FZ, Tachallait H, El Alaoui N-E, Talha A, Arshad S, Álvarez E *et al.* Ultrasound-assisted one-pot green synthesis of new N-substituted-5-arylidene-thiazolidine-2, 4-dione-isoxazoline derivatives using NaCl/Oxone/Na₃PO₄ in aqueous media. *Ultrasonics sonochemistry* 2020;68:105222.
 - Sandhu JS. Ultrasound-assisted synthesis of 2, 4-thiazolidinedione and rhodanine derivatives catalyzed by task-specific ionic liquid:[TMG][Lac]. *Organic and medicinal chemistry letters* 2013;3(1):1-6.
 - Gong K, He Z-W, Xu Y, Fang D, Liu Z-l. Green synthesis of 5-benzylidene rhodanine derivatives catalyzed by 1-butyl-3-methyl imidazolium hydroxide in water. *Monatshefte für Chemie-Chemical Monthly* 2008;139(8):913-915.
 - Jawale DV, Pratap UR, Lingampalle DL, Mane RA. Dicationic Ionic Liquid Mediated Synthesis of 5-Arylidene-2, 4-thiazolidinediones. *Chinese Journal of Chemistry* 2011;5(29):942-946.
 - Abbass SA, Moustafa GAI, Hassan HA, Abuo-Rahma GE-DA. Facile one-pot three-component synthesis of 4, 6-diaryl-3, 4-dihydropyrimidine-2 (1 H)-thiones under ultrasonic irradiation. *Synthetic Communications* 2019;49(21):2995-3000.
 - Cravotto G, Cintas P. Power ultrasound in organic synthesis: moving cavitation chemistry from academia to innovative and large-scale applications. *Chemical Society reviews* 2006;35(2):180-196.
 - Cella R, Stefani HIA. Ultrasound in heterocycles chemistry. *Tetrahedron* 2009;65(13):2619-2641.
 - Prakash O, Aneja DK, Lohan P, Hussain K, Arora S, Sharma C *et al.* Synthesis and antimicrobial activity of 5-((3-aryl-1-phenyl-1 H-pyrazol-4-yl) methylene) thiazolidine-2, 4-diones. *Medicinal Chemistry Research* 2012;21(10):2961-2968.
 - Youssef AM, White MS, Villanueva EB, El-Ashmawy IM, Klegeris A. Synthesis and biological evaluation of novel pyrazolyl-2, 4-thiazolidinediones as anti-inflammatory and neuroprotective agents. *Bioorganic & medicinal chemistry* 2010;18(5):2019-2028.
 - Sridhar S, Bhurta D, Kantiwal D, George G, Monga V, Paul AT. Design, synthesis, biological evaluation and molecular modelling studies of novel diaryl substituted pyrazolyl thiazolidinediones as potent pancreatic lipase inhibitors. *Bioorganic & medicinal chemistry letters* 2017;27(16):3749-3754.
 - Baiducci E, Attolino E, Taddei M. A Stereoselective and Practical Synthesis of (E)- α , β -Unsaturated Ketones from Aldehydes. *European journal of organic chemistry (Print)* 2011;(2):311-318.
 - Kumar BRP, Soni M, Kumar SS, Singh K, Patil M, Baig RBN *et al.* Synthesis, glucose uptake activity and structure-activity relationships of some novel glitazones incorporated with glycine, aromatic and alicyclic amine moieties *via* two carbon acyl linker. *European journal of medicinal chemistry* 2011;46(3):835-844.
 - Kumar BP, Nanjan M, Suresh B, Karvekar M, Adhikary L. 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. *Journal of heterocyclic chemistry* 2006;43(4):897-903.