International Journal of Pharmaceutical Sciences and Drug Analysis

E-ISSN: 2788-9254
P-ISSN: 2788-9246
IJPSDA 2021; 1(1): 18-25
Received: 11-01-2021
Accepted: 14-03-2021

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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, ^{1}H 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].

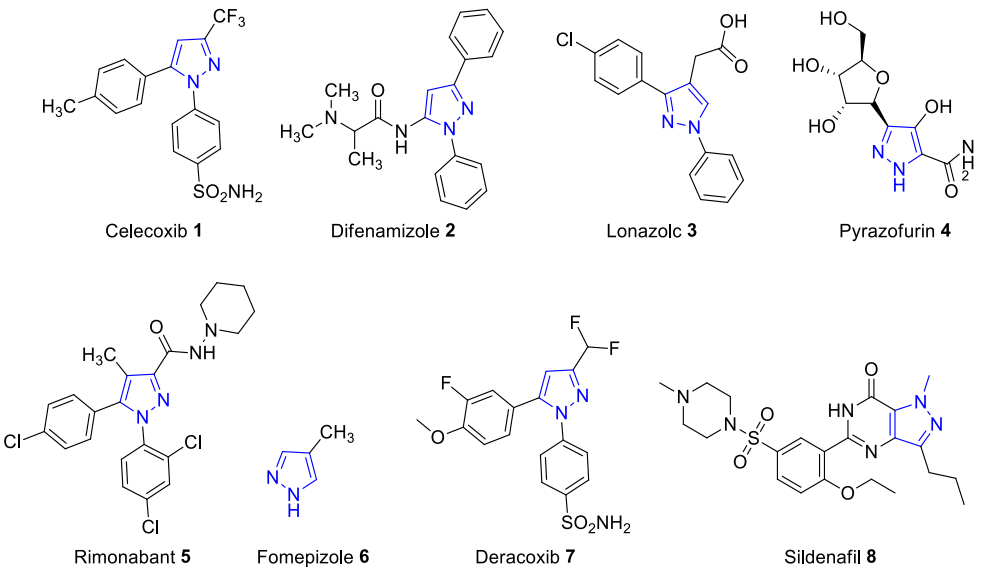


Fig 1: Representative examples of clinically used molecules having pyrazole framework

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).

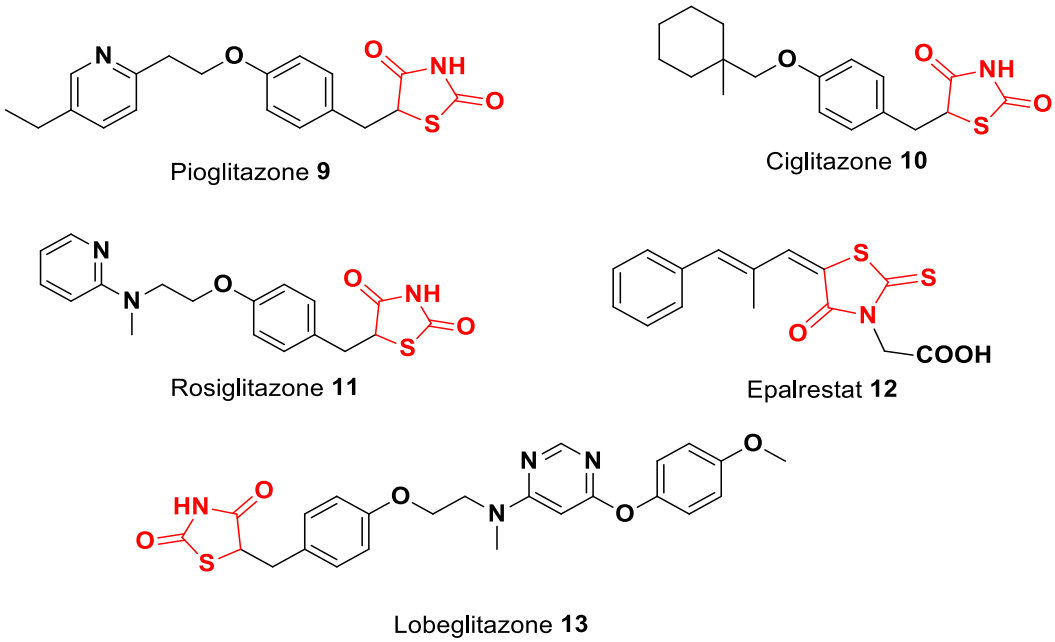


Fig 2: Clinically used molecules having 5-arylidene-2,4-thiazolidinedione derivatives

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.

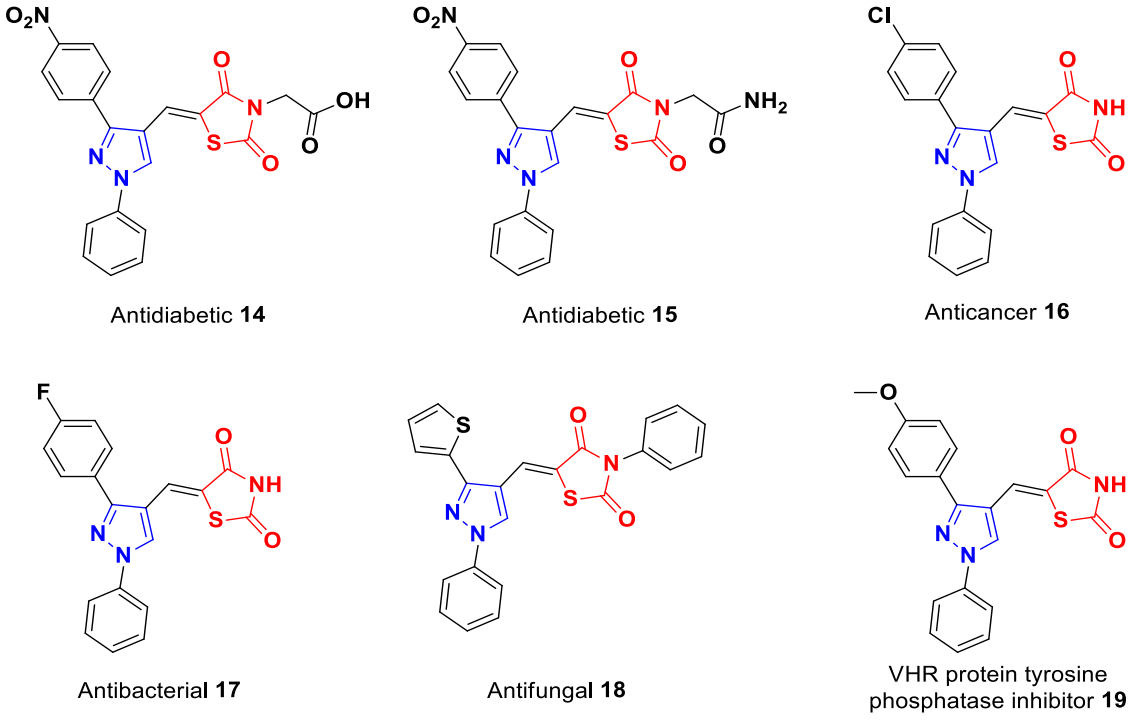


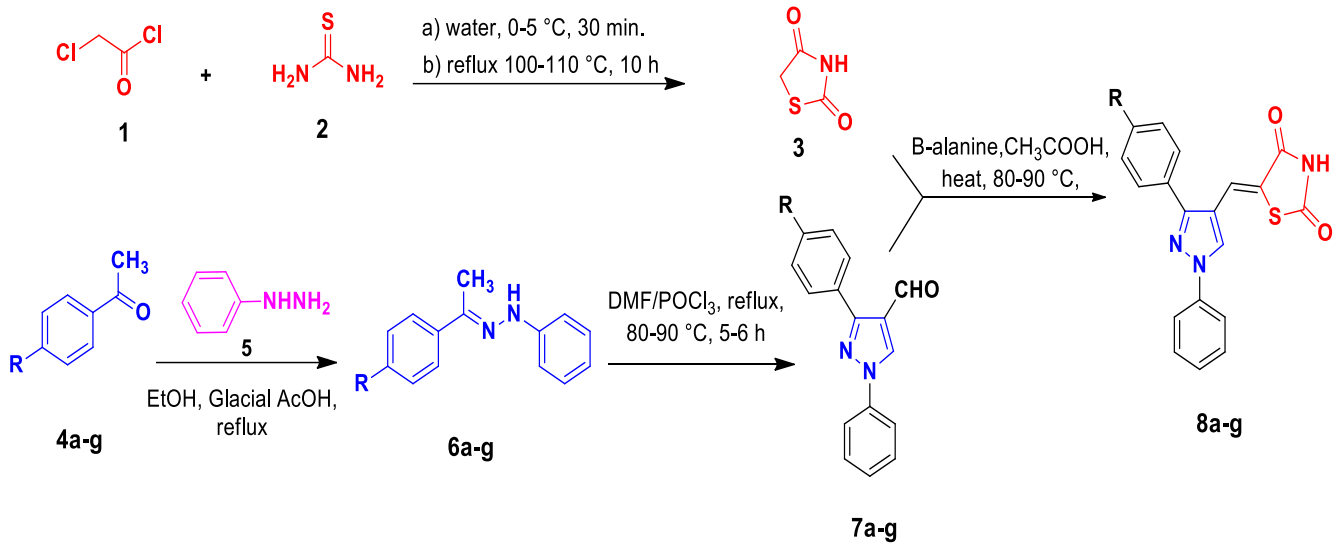
Fig 3: Representative example of biologically active pyrazole-2,4-thiazolidinedion derivatives

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-Al_2O_3, 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.

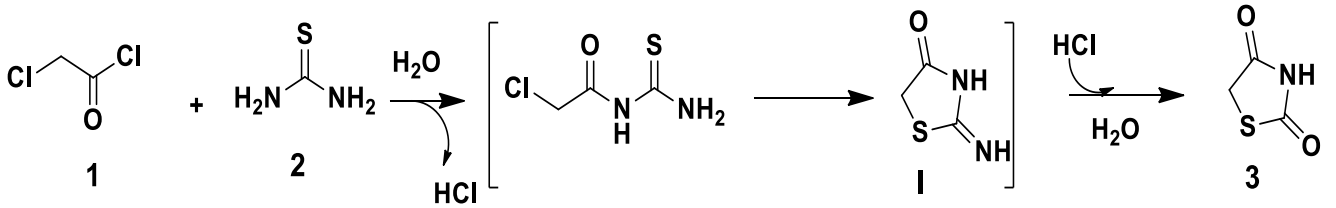


4a, 6a, 7a, 8a: R = H; 4b, 6a, 7b, 8b: R = CH_3; 4c, 6c, 7c, 8c: R = -OCH_3; 4d, 6d, 7d, 8d: R = Br; 4e, 6e, 7e, 8e: R = Cl; 4f, 6f, 7f, 8f: R = F; 4g, 6g, 7g, 8g: R = NO_2

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 form 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 $POCl_3$ to give pyrazolecarboxaldehydes 7a-g [25-27].

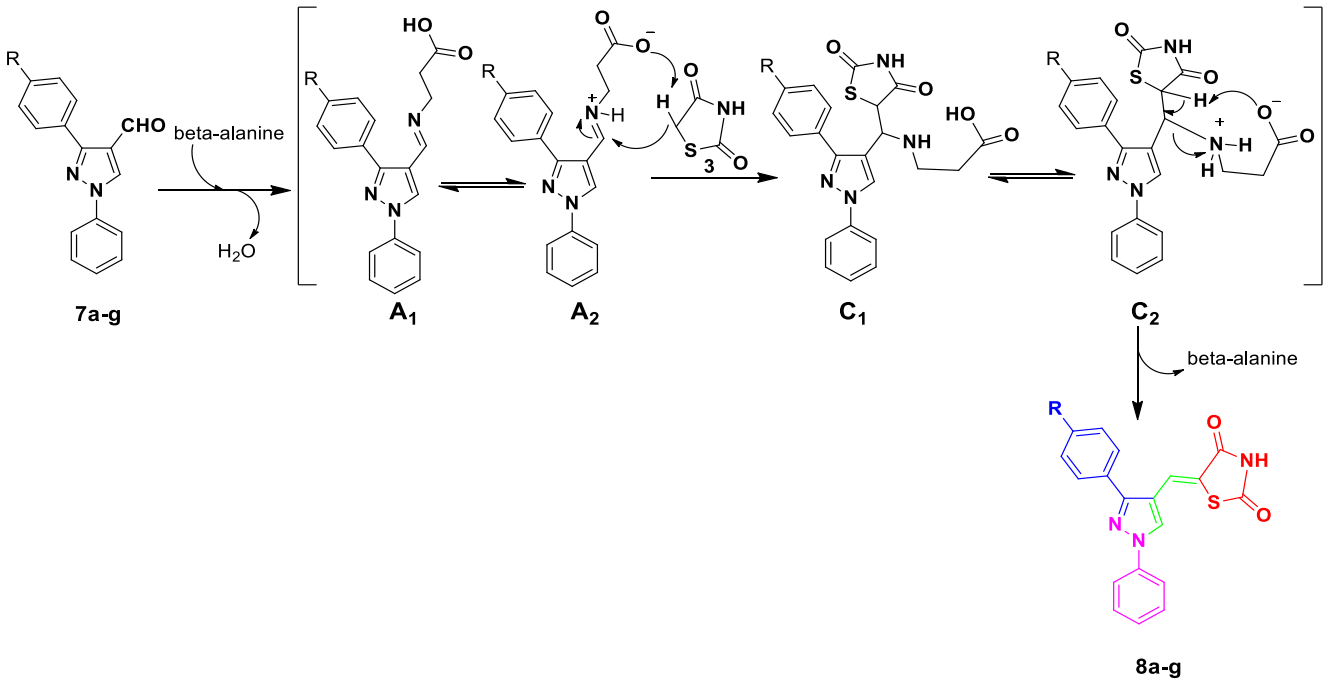
Further, to prepare the target diaryl substituted pyrazolyl-TZDs 8a-g, our initial pilot experiments have been achieved by using the conventional Knoevenagel condensation reaction between the synthesized pyrazolecarboxaldehydes and TZD to yield TZD clubbed pyrazole adducts 8a-g, however, the reaction 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) Method A	Yield (%)/ Time (min) 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 A_1 and TZD 3 gives rise to TZD anion. Meanwhile, aldehyde can form iminium ion A_2. The iminium ion A_2 condenses with TZD anion to form intermediate C_1 and C_2, 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 ^{13}C 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 consistence 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].

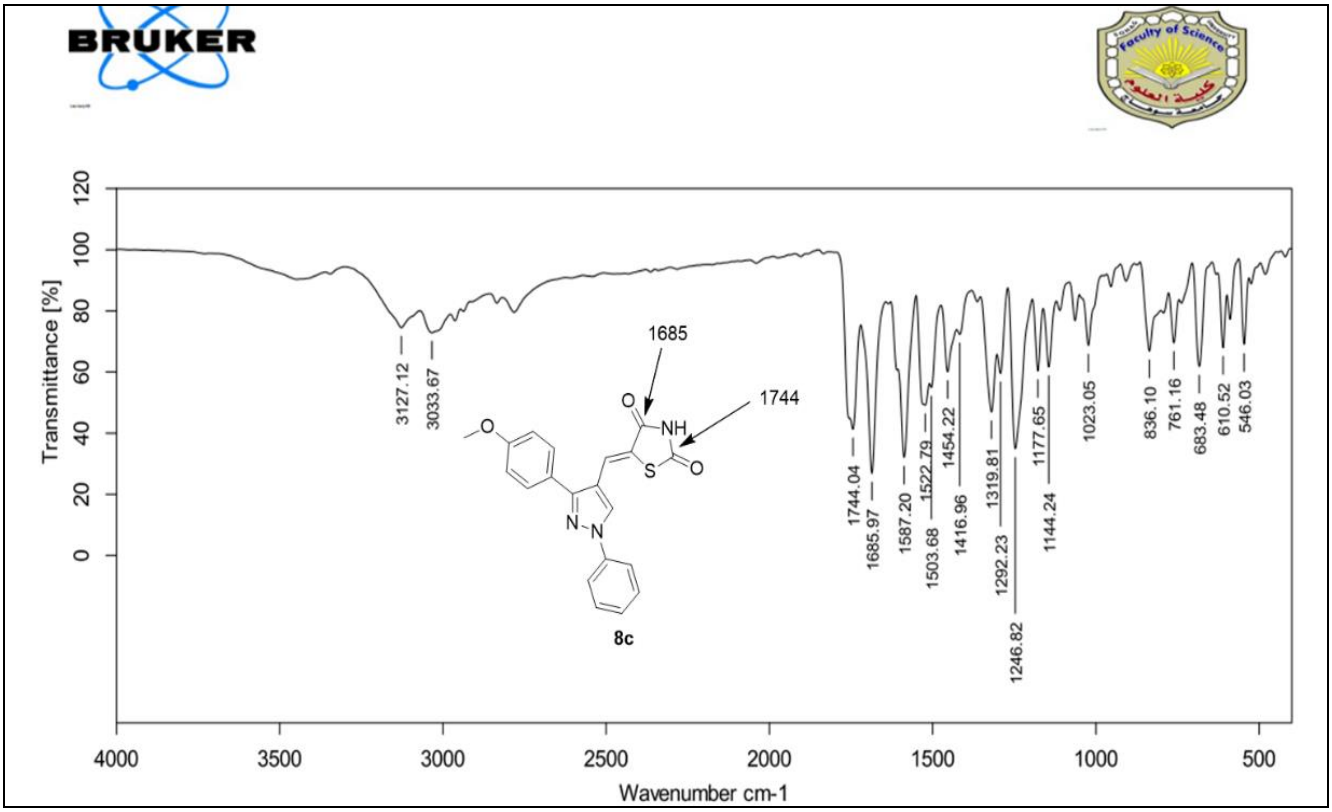


Fig 4a: Characteristics value of IR of compound 8c.

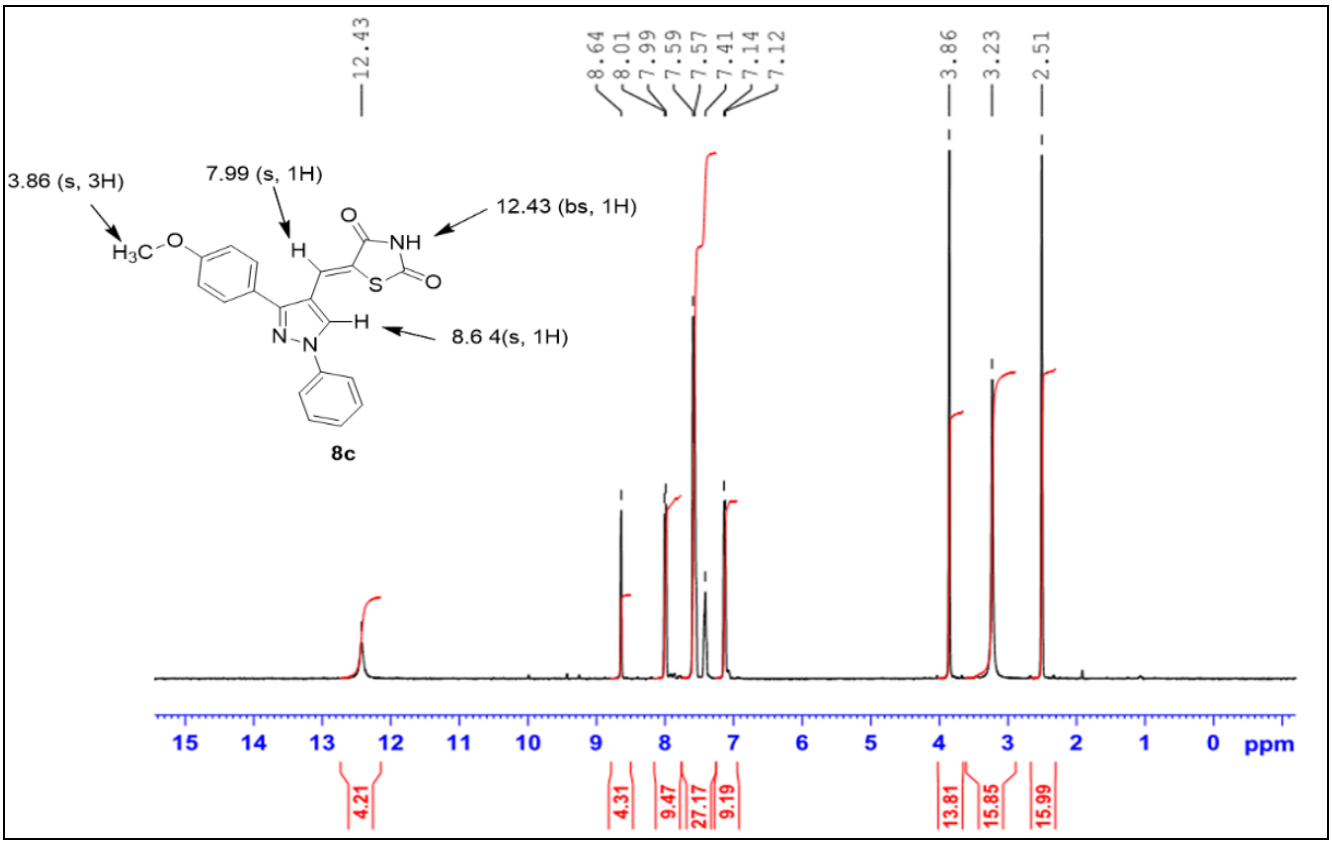


Fig 4b: Characteristics value of ^{1}H NMR of compound 8c.

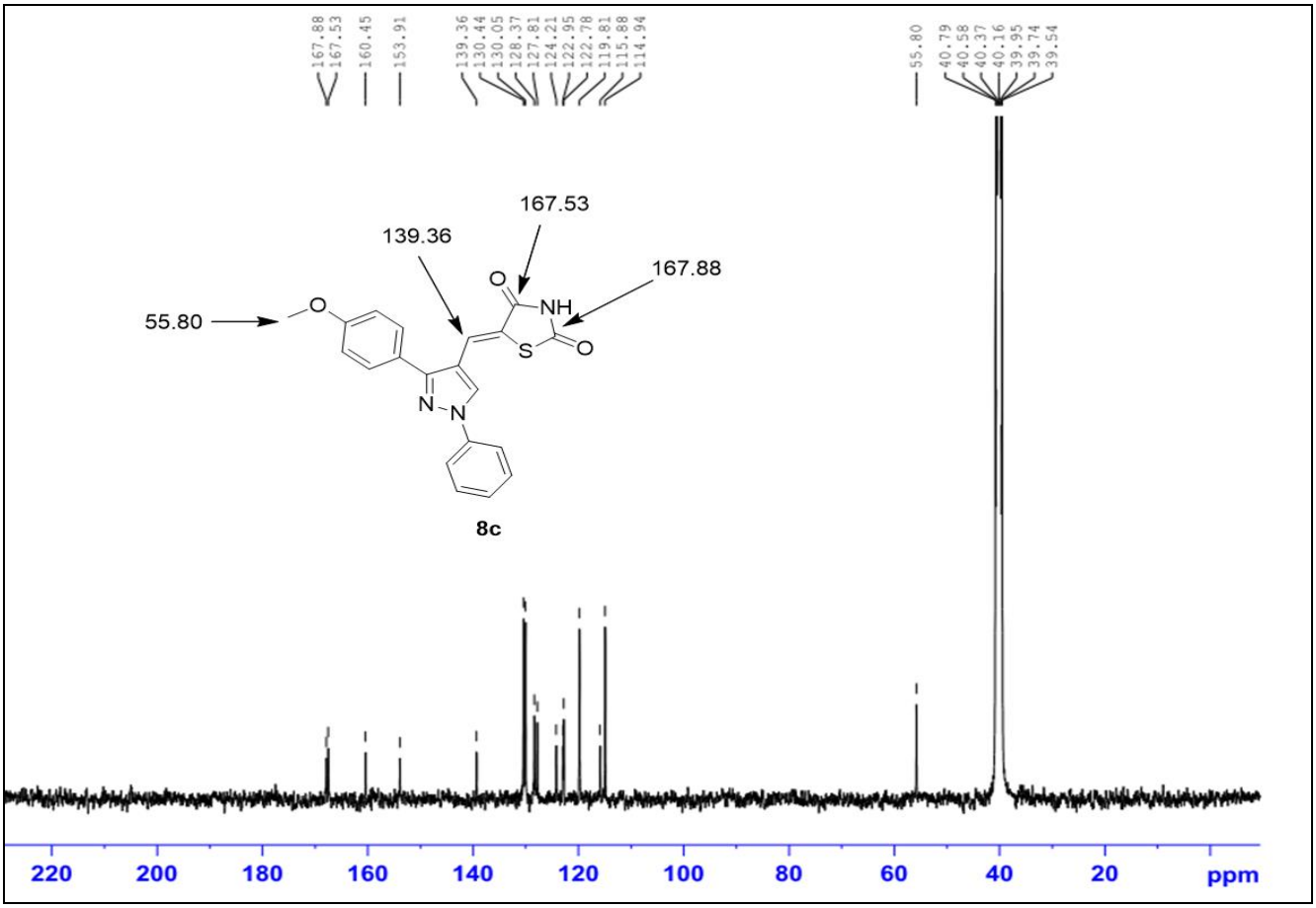


Fig 4c: Characteristics value of ^{13}C NMR and IR of compound **8c**.

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 ºC 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 ºC; 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 ºC; 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-1*H*-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-1*H*-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) $\nu_{max}cm^{-1}$: 1738 and 1688 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 12.51 (bs, IH, N-H, exch. D_2O); 8.71 (s, 1H, C_5-H of pyrazole); 8.02-8.00 (d, *J* = 8 Hz, 2H, ArH), 7.79-7.43 (m, 9H, Ar-H and -CH=C-); ^{13}C NMR (100 MHz, DMSO-d_6):δ (ppm) 168.36 (C_2=O), 167.16 (C_4=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 $C_{19}H_{13}N_3O_2S$: 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) $\nu_{max}cm^{-1}$: 1738 and 1688 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 12.62-12.51 (bs, 1H, N-H, exch. D_2O); 8.65 (s, 1H, C_5-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, CH_3); ^{13}C 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 $C_{20}H_{15}N_3O_2S$: 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) $\nu_{max}cm^{-1}$: 1744 and 1685 (C=O); ^{1}H NMR (400MHz, DMSO-d_6): δ (ppm) 12.4 (bs, IH, N-H, exch. D_2O); 8.64 (s, 1H, C_5-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, OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 167.88 (C_2=O), 167.53 (C_4=O), 160.45 (C-OCH_3), 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 $C_{20}H_{15}N_3O_3S$: 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) $\nu_{max}cm^{-1}$: 1754 and 1686 (C=O); ^{1}H NMR (400MHz, DMSO-d_6):δ (ppm) 12.29-12.25 (bs, IH, N-H, exch. D_2O); 8.65 (s, 1H, C5-H of pyrazole); 7.98-7.42 (m, 10 H, Ar-H and -CH=C-); ^{13}C NMR (100 MHz, DMSO-d_6):δ (ppm): 168.03 (C_2=O), 167.99 (C_4=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 $C_{19}H_{12}BrN_3O_2S$: 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) $\nu_{max}cm^{-1}$: 1739 and 1685 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 12.58-12.44 (bs, IH, N-H, exch. D_2O); 8.64 (s, 1H, C_5-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); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 167.82 (C_2=O), 167.51 (C_4=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 $C_{19}H_{12}ClN_3O_2S$: 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) $\nu_{max}cm^{-1}$: 1758 and 1696 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 12.64-12.52 (bs, IH, N-H, exch. D_2O); 8.69 (s, 1H, C_5-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); ^{13}C NMR (100 MHz, DMSO-d_6):δ (ppm) 168.21 (C_2=O),, 168.09 (C_4=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 $C_{19}H_{12}ClN_3O_2S$: 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) $\nu_{max}cm^{-1}$: 1750 and 1709 (C=O); ^{1}H NMR (400MHz, DMSO-d_6): δ (ppm) 12.5 (bs, IH, N-H, exch. D_2O); 8.75 (s, 1H, C_5-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); ^{13}C NMR (100 MHz, DMSO-d_6):δ (ppm) 167.75 (C_2=O), 167.52 (C_4=O), 151.50 (-C=N-), 148.11 (C-NO_2), 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 $C_{19}H_{12}N_4O_4S$: C, 58.16; H, 3.08; N, 14.28. Found: C, 58.04; H, 3.21; N-14.19%.

5. References

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