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Ultrasound promoted one-pot synthesis of 2-amino-4,8-dihydropyrano [3,2-*b*]pyran-3-carbonitrile scaffolds in aqueous media: A complementary 'green chemistry' tool to organic synthesis

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ABSTRACT

A green and simple approach to assembling of 2-amino-4,8-dihydropyrano[3,2-*b*]pyran-3-carbonitrile scaffolds via three-component reaction of kojic acid, malononitrile, and aromatic aldehydes in aqueous media under ultrasound irradiation is described. The combinatorial synthesis was achieved for this methodology with applying ultrasound irradiation while making use of water as green solvent. In comparison to conventional methods, experimental simplicity, good functional group tolerance, excellent yields, short routine, and selectivity without the need for a transition metal or base catalyst are prominent features of this green procedure.

1. Introduction

Green chemistry is a quickly developing new field that provides us a proactive path for the sustainable progress of future science and technologies [1]. Green chemistry uses highly efficient and environmental benign synthetic procedures to deliver life saving medicines, accelerating guide optimization processes in drug discovery, with reduced needless environmental impact. Green chemistry also offers enhanced chemical process economics concomitant with a reduced environmental burden [2]. In addition the use of green solvents like water shows both economical and synthetic advantages: not only the chemical processes needed to produce organic solvents will be reduced, the atmospheric pollution by escaping volatile organic solvents will be decreased and the waste treatment will be reduced, but also dramatic rate enhancements can be achieved in many organic reactions, that is Claisen rearrangement, aldol condensation, Diels–Alder cycloaddition [3]. The developing of new multi-component reactions (MCRs) and improving the known MCRs by ultrasonic irradiation are an area of considerable current interest. However, if the one-pot MCRs could be carried out under ultrasonic irradiation and catalyst-free conditions, it would be most efficient synthetic methods of organic synthesis [4]. As a one-pot reaction, ultrasound assisted multi-component reactions generally afford good yields in short reaction time and are fundamentally different from simple multi-component reactions in several aspects [5,6] and permitted a rapid access to combinatorial libraries of complex organic molecules for an efficient lead structure identification and optimization in drug discovery [7–9].

Ultrasonic-assisted organic synthesis (UAOS) as a green synthetic approach is a powerful technique that is being used more and more to accelerate organic reactions [10–14]. UAOS can be extremely efficient and it is applicable to a broad range of practical syntheses. The notable features of the ultrasound approach are enhanced reaction rates, formation of purer products in high yields, easier manipulation and considered a processing aid in terms of energy conservation and waste minimization which compared with traditional methods, this technique is more convenient taking green chemistry concepts into account [15,16]. However, the use of ultrasound in heterocyclic system is not fully explored [17,18].

Polysubstituted 2-amino-4*H*-pyran-3-carbonitrile derivatives are very important heterocyclic compounds, which frequently exhibit a variety of biological activities [19–24]. Recently, several methods have been reported for the facile and efficient synthesis of important polysubstituted 2-amino-4*H*-pyran-3-carbonitrile scaffolds [25–28]. Any of these methods, however, suffer from longer reaction times, unsatisfactory yields, harsh reaction

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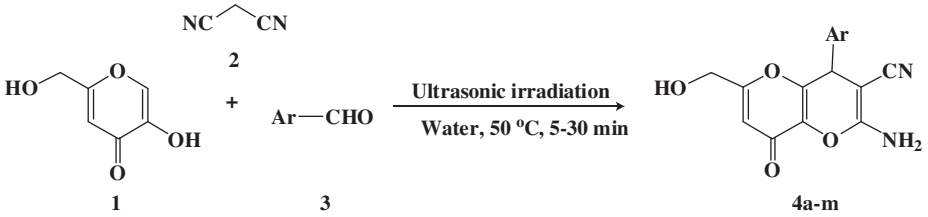
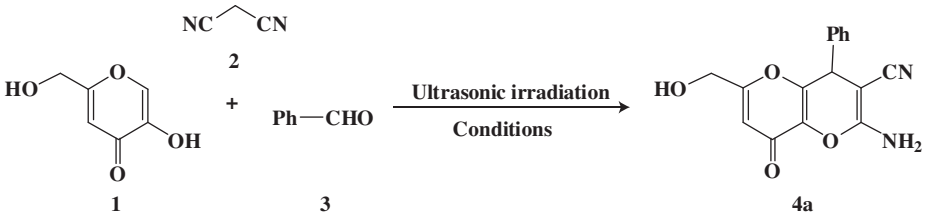


Scheme 1. Synthesis of 2-amino-4,8-dihydropyrano[3,2-*b*]pyran-3-carbonitriles in water under ultrasonic irradiation.



Scheme 2. Standard model reaction.

conditions and excessive use of reagents and catalysts. It is therefore important to find more convenient methods for the preparation of these compounds. Among these compounds, the ready availability, potential biological activity and high reactivity of kojic acid makes it an attractive molecule in pharmaceutical chemistry and multi-component reactions [29,30]. Consequently, a large number of kojic acid derivatives have been prepared for biological evaluation [31,32]. The combination of two important scaffolds such as kojic acid and pyran, may lead to new and alternative drug candidates with improved pharmacological profile.

In continuation of our interest in exploring the synthetic of heterocyclic compound in water [33,34], the broad spectrum of applications of kojic acid **1** and its derivatives as biologically active compounds, has prompted us to explore its reaction with malononitrile **2**, aldehydes **3** in a mild and efficient three-component reaction in aqueous media under ultrasound irradiation (Scheme 1).

2. Experimental

All reagents were purchased from Merck (Germany) and were used without further purification. Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. Infrared (IR) spectra were recorded using a Perkin-Elmer FT-IR 550 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded with a Bruker DRX-400 spectrometer at 400 and 100 MHz respectively. NMR spectra were obtained in DMSO-d_6 solutions and are reported as parts per million (ppm) downfield from a tetramethylsilane internal standard. The following abbreviations are used; singlet (s), doublet (d), triplet (t) and multiplate (m). The element analyses for C, H, and N were performed using a Carlo ERBA Model EA 1108 analyzer carried out on Perkin-Elmer 240c analyzer, Sonication was performed in Shanghai Branson-BUG40-06 ultrasonic cleaner (with a frequency of 40 kHz and a nominal power 200 W).

2.1. Typical procedure for the synthesis of 2-amino-4,8-dihydropyrano[3,2-b]pyran-3-carbonitriles (4a) in water under silent conditions

A 50 mL flask was charged with malononitrile (66 mg, 1 mmol), benzaldehyde (1 mmol), and kojic acid (1 mmol) in water (5 mL). The mixture was stirred at 50 °C. After the completion of the reaction (monitored by TLC), the reaction was allowed to cool. The residue was filtered and was recrystallized from ethanol to produce the desired product **4a** as white solid in 75% yield.

2.2. Typical procedure for synthesis of 2-amino-4,8-dihydropyrano[3,2-b]pyran-3-carbonitriles (4a) under ultrasound irradiation

A 25 mL Erlenmeyer flask was charged with malononitrile (66 mg, 1 mmol), benzaldehyde (1 mmol), and kojic acid (1 mmol) and water (5 mL). The reaction flask was located in the ultrasonic bath, where the surface of reactants is slightly lower than the level of the water, and irradiated under 20%, 40%, 60%, 80% and 100% of the power of the ultrasonic bath at 50 °C (bath temperature, the temperature inside the reactor was also 50 °C) for the period of time (The reaction was monitored by TLC) separately as indicated in Table 3. The reaction temperature was controlled by addition or removal of water from ultrasonic bath. After completion of the reaction, the mixture was diluted with water (10 mL), the solid was filtered, washed with water and dried to give crude product, which was further purified by recrystallization from ethanol to offer pure product **4a** in 95% yield.

3. Results and discussions

To achieve the suitable conditions for the synthesis of 2-amino-4,8-dihydropyrano [3,2-*b*]pyran-3-carbonitriles, various reaction conditions have been investigated in the standard reaction of kojic acid **1**, malononitrile **2**, and benzaldehyde **3a** as a model reaction (Scheme 2).

3.1. Effects of the solvents under ultrasound irradiation

Initially, we try to optimize the model process mentioned above by detecting the efficiency of several classic solvents chosen as the medium for comparison through some experiments. In each case, the substrates were mixed together with 5 ml solvent under ultrasonic irradiation (power intensity: 40%). Among the tested solvents such as methanol, ethanol, acetonitrile, THF, dichloromethane, water and solvent-free conditions, the formation of product **4a** was more facile and proceeded to give not only in high yield but also with high reaction rate in water (78 yield in 25 min) (Table 1, **entry 7**). Polar protic solvents such as ethanol and methanol

Table 1
The effect of reaction condition on the synthesis of **4a** under various conditions.[a]

Entry	Solvent	Temperature (°C)	Time (min)	Isolated yield (%)	
				A	B
1	Ethanol	30	50	70	55
2	Methanol	30	55	60	52
3	Acetonitrile	30	120	45	Trace
4	Dioxane	30	90	45	25
5	DCM	30	130	35	Trace
6	Solvent-free	30	85	50	30
7	Water	30	25	78	50
8	Water	50	20	88	75
9	Water	60	20	88	74
10	water	70	20	80	74

[a] Substrate: kojic acid (1 mmol), malononitrile (1 mmol), benzaldehyde (1 mmol), and solvent (5 mL); Conditions: **A**, under ultrasonic irradiation with power intensity of 40%; **B**, under high stirring condition.

afforded moderate yields of desired products but took comparatively longer reaction time (Table 1**, entries 1 and 2**). When the reaction was performed in acetonitrile, dioxane and dichloromethane, unfortunately, the desired product was only obtained in 45%, 45% and 35% yield respectively (Table 1**, entries 3, 4, 5**). In solvent-free conditions the desert products 4a was obtained in low yield 50% (Table 1**, entry 6**).

In order to verify the effect of ultrasound irradiation, the reaction was also performed in mentioned solvents by high stirring alone under silent condition (Table 1). As shown in Table 1, in all cases, the experimental results show that the yields of the products are lower than sonication within same reaction times. Based on the results of this study, it's clear that the ultrasound improves the yields of products. According to our opinion, the possible nuclei for occurrence of cavitation in water to other solvents can be done faster and wider. Also the transfer of ultrasonic energy in water is higher than in other solvents. Therefore water was chosen as solvent of reaction.

3.2. Effects of reaction temperature under ultrasonic irradiation

To study the effect of temperature on this synthesis, we investigated the model reaction at different temperatures. The product was obtained in yields ranging from 78% to 88% (Table 1**, entries 7–10**). It was observed that a lower reaction temperature led to a lower yield. As shown in Table 1, entry 7, we found that high temperature could improve the reaction yield and shorten the reaction time. It can be seen from the results that with increasing media temperatures, the formation of product increased rapidly in 30 to 50 °C in terms of reaction time and yield. One reason is possibly due to the decrease of the surface tension and viscosity of the solution, so that the generations of bubbles become easier. Another is the increment kinetic energy of liquid due to increase of temperature convert into heating contents of bubbles that caused to relatively higher yield and shorter reaction time. On the other hand with increasing of temperature from 60 to 70 °C, the yield was decreased to 89% (Table 1**, entries 9 and 10**). Probably, a higher reaction temperature might induce a decrease in cavities growth, lifetime and results in a dramatic increase of the vapor pressure of the liquid, which results in higher vapor content of the cavitating bubbles. Under these conditions, the maximum temperature and pressure created in such vaporous transient cavitation bubbles have been shown to be much lower [35]. With having these results in hand, we selected the water as solvent under ultrasound irradiation conditions for the one-pot reaction of malononitrile, benzaldehyde derivatives, and kojic acid to give corresponding 2-amino-4,8-dihydropyrano[3,2-*b*]pyran-3-carbonitriles at 50 °C. These results were indicated that there was remarkable ultrasonic temperature effect on this reaction.

3.3. Effect of intensity power of ultrasonic on reaction

After this, we have studied the effect of the ultrasound power intensity; the reaction was also performed at 20%, 40%, 60%, 80% and 100% of the rate power of the ultrasonic bath (40, 80, 120, 160 and 200 W). The results were showed in Table 2. Generally,

Table 2
The effect of ultrasonic power on the synthesis of **4a**.

Max power intensity (W)	20% (40 W)	40% (80 W)	60% (120 W)	80% (160 W)	100% (200 W)
Time (min)/Yield (%)[a]	25/75	20/88	10/95	10/95	10/90

[a] Isolated yields.

Table 3
Synthesis of 2-amino-4,8-dihydropyrano[3,2-*b*]pyran-3-carbonitrile derivatives under sonication and conventional conditions.[a]

Entry	Product	Ar	With sonication[a]		Without sonication[b]	
			Time (min)	Yield (%)[c]	Time (h)	Yield (%)[c]
1	**4a**	C_6H_5	10	95	1.2	79
2	**4b**	2-FC_6H_4	20	85	3.0	-[d]
3	**4c**	2-ClC_6H_4	25	88	3.0	-[d]
4	**4d**	2,4-$Cl_2C_6H_3$	25	89	3.0	-[d]
5	**4e**	3-FC_6H_4	15	93	2.5	65
6	**4f**	3-MeC_6H_4	5	97	1.0	68
7	**4g**	3-BrC_6H_4	15	95	1.7	67
8	**4h**	3,5-$(MeO)_2C_6H_3$	5	96	2.5	53
9	**4i**	4-FC_6H_4	6	98	1.5	60
10	**4j**	3-Pyridyl	5	98	1.2	56
11	**4k**	4-Pyridyl	15	90	2.0	55
12	**4l**	2-Furyl	5	98	1.5	60
13	**4m**	2-Thienyl	6	97	1.0	62

[a] Reaction condition: reaction of aryl or heteroaryl aldehydes, malononitrile, kojic acid in water at 50 °C under ultrasound irradiation.
[b] Reaction condition: reaction of aryl or heteroaryl aldehydes, malononitrile, kojic acid in water at 50 °C under high stirring condition.
[c] Yields of isolated products.
[d] Only obtained the intermediate benzylidenemalononitrile.

increase of ultrasonic power means that higher intensity of ultrasound was introduced into the reaction vessel, which would accelerate the reactions. It can be seen from Table 2 that increase of ultrasonic power led to relatively higher yield and shorter reaction time before the ultrasound power intensity reached 80%, and then the yield decreased slightly with increasing ultrasound power intensity.

As we know, more energy was provided to reaction system to accelerate cavitation effect with ultrasonic power increasing. The increase in the acoustic power could increase the number of activecavitation bubbles and also the size of the individual bubbles. Both increases can be expected to result in an increase in the maximum collapse temperature [35], and the respective reaction could be accelerated. However, when ultrasonic intensity exceeded the optimal value, a large number of gas bubbles exist in the solution and a lesser level of energy is focused on the reaction vessel because of the scattering effect of gas bubbles on the sound waves. On the other hand, it is possible the coalescence of the cavities in the presence of large number of cavities resulting in the formation of a large cavity which collapses less violently. So with the inordinate increase in the operating intensity, the utilization efficiency of ultrasound decrease and the reaction yield decreased too [35].

3.4. High efficiency and generality of synthesis by ultrasound irradiation

In order to demonstrate the efficiency and scope of the present method and to delineate the role of ultrasound, this methodology was examined by the reaction of several substituted aryl or heteroaryl aldehydes, malononitrile, and kojic acid with and without ultrasonic irradiation at the same temperature (50 °C) in water (Table 3). When the reaction was carried out under conventional method it gave comparatively low yields of products and took longer reaction time, while the same reaction carried in the influence of ultrasonic irradiation gave excellent yields of product in short reaction time (Table 3). Thus, ultrasonic irradiation was found to have beneficial effect on the synthesis of 2-amino-4,8-dihydropyrano[3,2-*b*]pyran-3-carbonitrile derivatives which was superior to the traditional method with respect to yield, reaction time. From the results shown in Table 3, it is evident that electron-rich aromatic aldehydes afford fairly high yields of the desired products than electron-deficient ones in reaction with malononitrile, and kojic acid under ultrasonic irradiation in water at 50 °C.

The results in Table 3 highlight a variety of structures accepted by the method to give fairly excellent yields of the desired products, the scope of the method is expected to be even wider due to its mild conditions with applying ultrasonic energy without any base, or acid catalysts. Through the experiments mentioned above, it was observed that there was a great amount of liquid in this system originally because of the bad solubility benzaldehyde in water at 50 °C. As the reaction went on under sonication, the reactants were gradually dispersed in the reaction solvent and then disappeared after about 5 min, while the classical condition needs 1 h. When the reaction was over (monitored by TLC), more and more solids had appeared which TLC spot (RF) was different with that of benzaldehyde. After separation and analysis such as ^{1}H NMR, it was surprising to find that the product is the desired one. Then, we put two experiments to further study the acceleration mechanism under sonication. After dissolution of insoluble substrates which were irradiated under sonication, we carry out the comparison between with and without ultrasound. We found that the reaction without sonication for follow-up process took a long time and the yields were relatively low. In the heterogeneous reactions involving immiscible liquid, the reaction between these species can only occur in the interfacial region between the liquids. Sonication can be used to produce very fine emulsions from immiscible liquids. This is possible because cavitational collapse at or near the interface disrupts it and impels jets of one liquid into the other to form the emulsion [10]. These can cause the reaction to take place rapidly. Therefore, in the present system, ultrasound was found to have beneficial effect on solubility behavior and the synthesis of **4a**.

The structures of isolated new products **4a-m** were deducted by physical and spectroscopic data such as: IR, ^{1}H NMR and ^{13}C NMR spectroscopy, and elemental analysis [36]. In IR spectra, symmetrical and unsymmetrical stretching frequency of NH_2 is formed in region between $\nu = 3330–3350\ Cm^{-1}$. The stretching vibration of C≡N in nitrile group was appeared in the region between $\nu = 2190–2210\ Cm^{-1}$. In the ^{1}H NMR spectra in DMSO-d_6 was shown the two singlet signals around $\delta = 7.2–7.35$ and $\delta = 4.60–4.80$ ppm corresponding to NH_2 group and Ar–C–H pyran ring in 2-amino-4,8-dihydropyrano [3,2-*b*]pyran-3-carbonitriles was confirmed the formation of desired products in reaction (Fig. 1).

In the H–H COSY spectra (Fig. 2) in DMSO-d_6 was shown the two coupled signals around $\delta = 4.10–4.30$ and $\delta = 5.50–5.80$ ppm corresponding to CH_2 and OH group of compound **4f**. The methylene group on the methylenoxy substituent shows a rather more complex splitting pattern than a simple doublet. This behavior is due to a non-equivalence of the two hydrogens of the methylene group. As shown, the diastereotopic hydrogens of methylene group were found as coupling partners on both the vertical and the horizontal lines from the hydrogen of OH with coupling constant of $^3J_{vic} = 6.3$ Hz (Fig. 2).

3.5. The study of acceleration mechanism under irradiation of ultrasound

We have not established an exact mechanism for the formation of 2-amino-4,8-dihydropyrano[3,2-*b*]pyran-3-carbonitriles, however, a plausible mechanism explaining the aforementioned results and the selectivity is depicted in Scheme 3. The reaction is thought to proceed through Knoevenagel condensation, Michael addition, and a cyclocondensation, which might initiate via two pathways, namely A and B (Scheme 3). The effect of ultrasonic irradiation can be foreseen when considering the following step where the cyclization of 9 or 10 occur via a dipolar transition states **TS1** and **TS'1** amenable to establish favored interaction with the ultrasound in hot cavities. Thus, ultrasound irradiation activates the reaction mixture by inducing high local temperatures and pressure generated inside the cavitation bubble and its interfaces when it collapses and accelerates the reaction rate and shortens the reaction time. Also this phenomena, cavitation, cause to remove water in condensation and cyclization steps and accelerate reaction in water efficiently. Cavitation is the origin of sonochemistry, a physical process that creates, enlarges, and implodes gaseous and vaporous cavities in an irradiated liquid, thus enhancing the mass transfer and allowing chemical reactions to occur. The creation of the so-called hot spots in the reaction mixture produces intense local temperatures and high pressures generated inside the cavitation bubble and its interfaces when it collapses. Therefore the very reactive chemical species such as 7, 8 with short lifetime giving rise to the 2-amino-4,8-dihydropyrano[3,2-*b*]pyran-3-carbonitriles (**4a–m**) in shorter times under ultrasound irradiation, thus facilitating the cyclization, and dehydration step that is critical in this type of multi-component reactions. Furthermore, compared with traditional methods, this technique is more efficient and environmental-friendly, particularly when considering the basic green chemistry concepts. It is noteworthy to mention that, the effect of the nature of the substituent on the aromatic aldehydes ring showed obvious effect on this conversion. The electron-releasing groups not only obvious effect on the yield of this conversion but also effect on the reaction time (Table 3**, entries 6, 10**). The

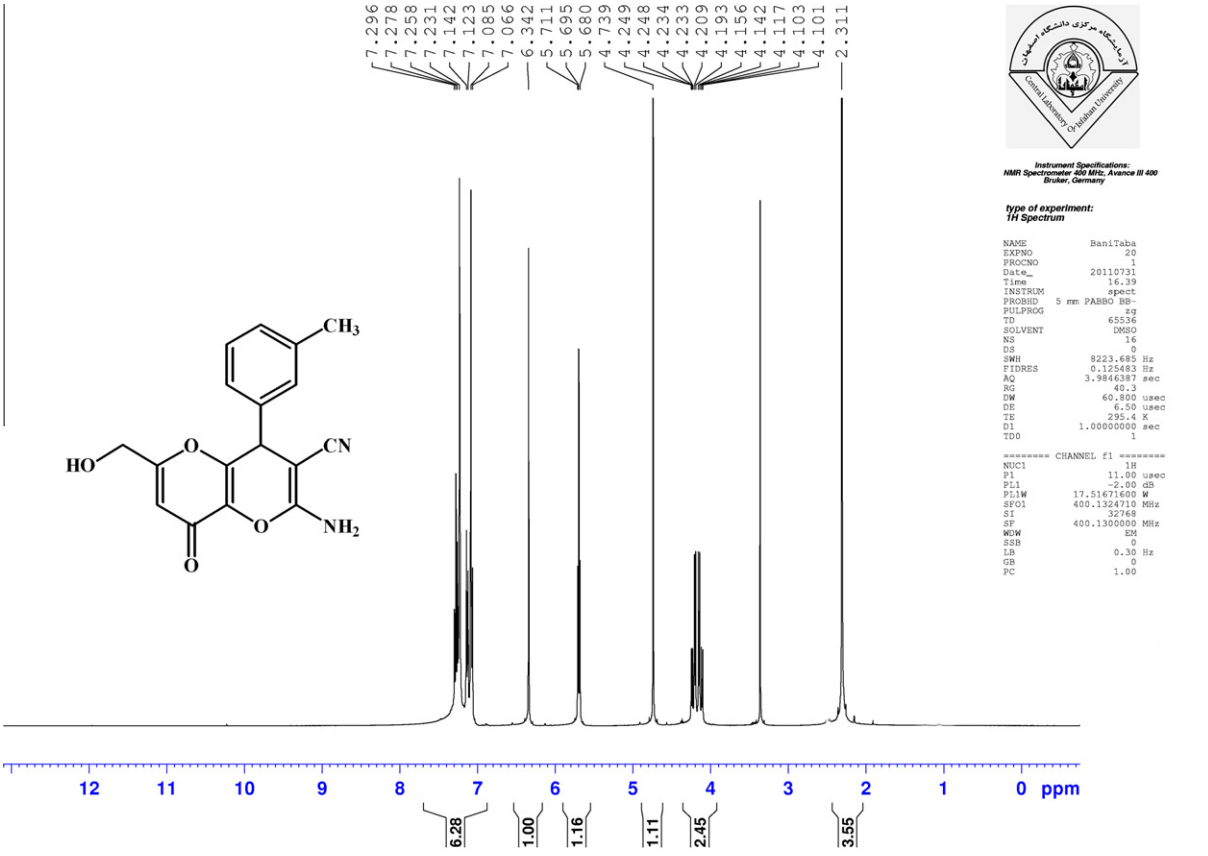


Fig. 1. ^{1}H NMR spectra of compound **4f**.

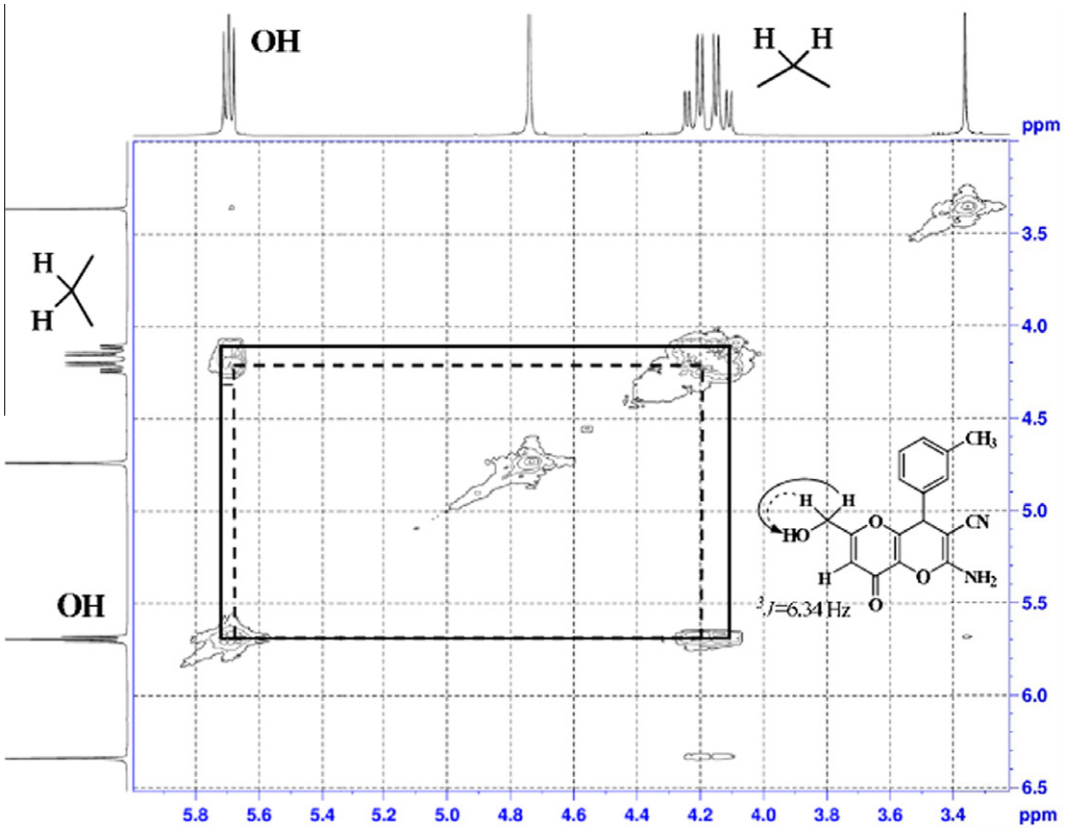
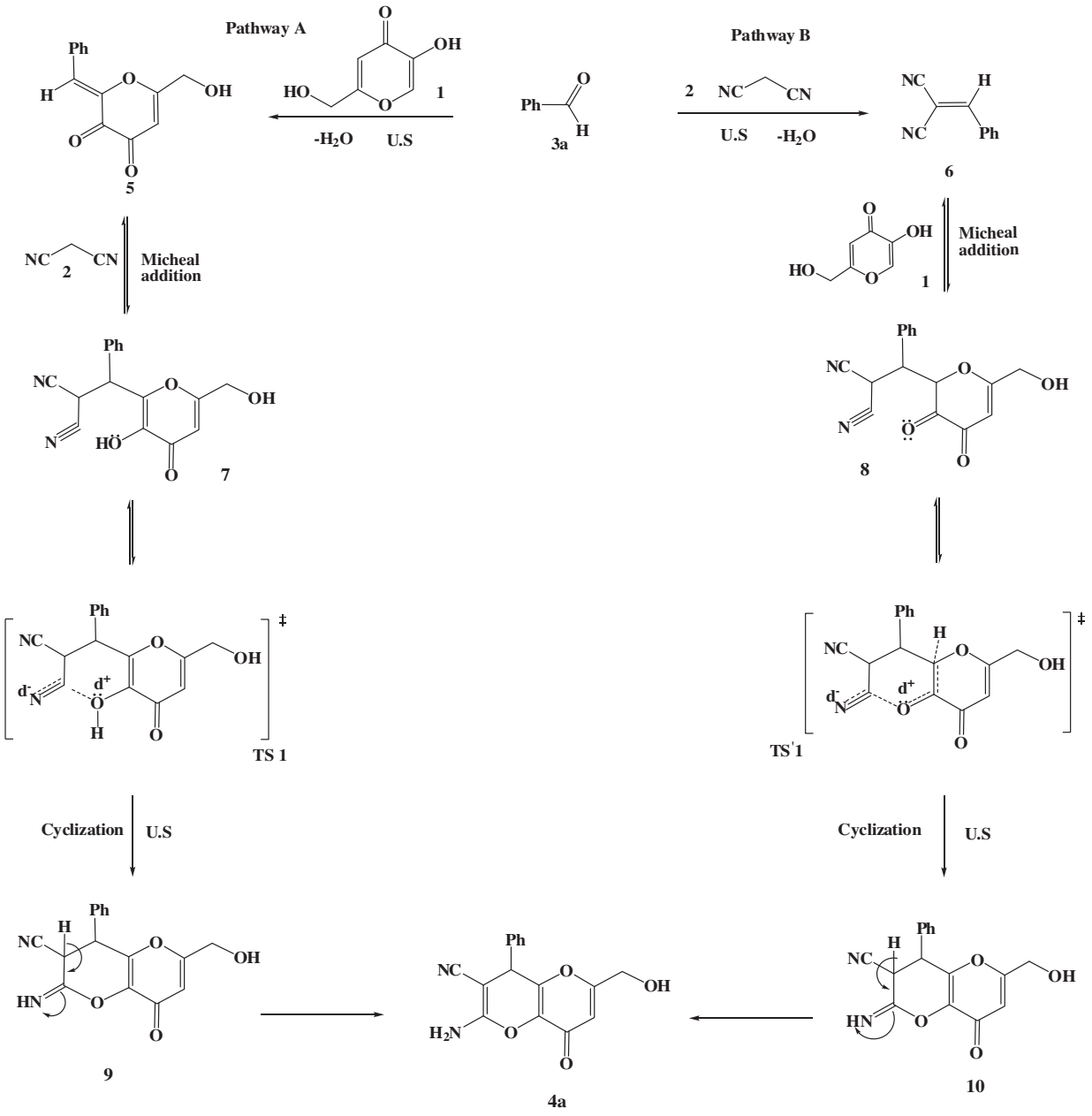


Fig. 2. Hydrogen's correlation in H–H COSY of product **4f**.



Scheme 3. Plausible mechanism of the reaction.

electron-releasing groups on aromatic aldehydes ring facile Michael addition of malononitrile to (*E*)-2-benzylidene-6-(hydroxymethyl)-2*H*-pyran-3,4-dione **5** in pathway A or kojic acid to **6** in pathway B.

4. Conclusion

In conclusion, we have reported an environmentally benign method for the synthesis of 2-amino-4,8-dihydropyrano[3,2-*b*]pyran-3-carbonitrile derivatives via three-component reaction of arylaldehydes, malononitrile, and kojic acid in water at 50 °C under ultrasound irradiation. This method provides several advantages such as environmental friendliness, shorter reaction time, excellent yields, no requirement base, earth metal Lewis acid, and simple workup procedure. We expect this method will find extensive applications in the field of combinatorial chemistry, diversity-oriented synthesis, sonochemistry, and drug discovery.

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[36] Data spectra of products: compound **4a**: Colorless crystals; m.p = 220–222 °C; IR (KBr, ν, Cm^{-1}): 3353 and 3361 (NH_2), 3340 (OH), 2218 (CN), 1460 (C=O) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ = 4.14 (dd, 1H, ^2J = 15.1, ^4J = 6.0 Hz, CH_{aliph}), 4.23 (dd, 1H, ^2J = 15.1, ^4J = 6.0 Hz, CH_{aliph}), 5.23 (t, 1H, ^4J = 6.0 Hz, OH), 5.62 (s, 1H, CH_{vinyl}), 6.29 (s, 1H, CH_{aliph}), 7.11 (s, 2H, NH_2), 7.22-7.50 (m, 5H, CH_{arom}); ^{13}C NMR (100 MHz, DMSO-d_6) δ_c = 45.3, 58.6, 111.2, 117.9, 118.2,128.5, 130.5, 132.2, 136.5, 137.7, 147.9, 158.3, 168.2, 169.2, 194.2; Anal. Calcd. for $C_{16}H_{12}N_2O_4$: C, 64.92; H, 4.12; N, 9.44. Found: C, 64.86; H, 4.08; N, 9.46. Compound **4b**: Colorless crystals; m.p = 207–208 °C; IR (KBr, ν, Cm^{-1}): 3352 and 3365 (NH_2), 3349 (OH), 2220 (CN), 1465 (C=O)cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ = 4.13 (dd, 1H, ^2J = 15.2, ^4J = 5.6 Hz, CH_{aliph}), 4.25 (dd, 1H, ^2J = 15.2, ^4J = 5.6 Hz, CH_{aliph}), 4.91 (t, 1H, ^4J = 5.6 Hz, OH), 5.71 (s, 1H, CH_{vinyl}), 6.36 (s, 1H, CH_{aliph}), 7.11 (s, 2H, NH_2), 7.36 (m, 4H, CH_{arom}); ^{13}C NMR (100 MHz, DMSO-d_6) δ_c = 54.4, 59.1, 111.4, 115.5 (d, ^2J = 21.0 Hz, C–F), 119.3, 125.8 (d, ^2J = 12.0 Hz, C-F), 127.3, 130.2 (d, ^3J = 8.0 Hz, C-F), 130.4 (d, ^3J = 4.0 Hz, C-F), 136.7, 147.9, 159.3, 159.5, 168.2, 169.5, 195.3; Anal. Calcd. for $C_{16}H_{11}FN_2O_4$: C, 61.23; H, 3.59; N, 8.93. Found: C, 61.15; H, 3.53; N, 8.91. Compound **4c**: Colorless crystals; m.p = 210-213 °C; IR (KBr, ν, Cm^{-1}): 3371 and 3331 (NH_2), 3351 (OH), 2217 (CN), 1613 (C=O) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ = 4.19 (dd, 1H, ^2J = 15.3, ^4J = 6.0 Hz, CH_{aliph}), 4.22 (dd, 1H, ^2J = 15.3, ^4J = 6.0 Hz, CH_{aliph}), 5.27 (t, 1H, ^4J = 6.0 Hz, OH), 5.68 (s, 1H, CH_{vinyl}), 6.36 (s, 1H, CH_{aliph}), 7.14 (s, 2H, NH_2), 7.20-7.50 (m, 4H, CH_{arom}); ^{13}C NMR (100 MHz, DMSO-d_6) δ_c = 54.6, 59.0, 111.4, 118.9, 128.1, 129.7, 130.1, 130.8, 132.2, 136.9, 137.4, 147.9, 159.4, 168.2, 169.5, 194.9; Anal. Calcd. for $C_{16}H_{11}ClN_2O_4$: C, 58.21; H, 3.40; N, 8.49. Found: C, 58.11; H, 3.35; N, 8.47. Compound **4d**: Colorless crystals; m.p = 240-242 °C; IR (KBr, ν, Cm^{-1}): 3465 and 3353 (NH_2), 3560 (OH), 2211 (CN), 1609 (C=O) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ = 4.13 (dd, 1H, ^2J = 15.3, ^4J = 6.0 Hz, CH_{aliph}), 4.21 (dd, 1H, ^2J = 15.3, ^4J = 6.0 Hz, CH_{aliph}), 5.28 (t, 1H, ^4J = 6.0 Hz, OH), 5.68 (s, 1H, CH_{vinyl}), 6.35 (s, 1H, CH_{aliph}), 7.34 (s, 2H, NH_2), 7.44 (d, 1H, ^3J = 8.4 Hz, CH_{arom}), 7.67 (d, 1H, ^4J = 2.4 Hz, CH_{arom}), 7.82 (dd, 1H, ^3J = 8.4, ^4J = 2.0 Hz, CH_{arom}); ^{13}C NMR (100 MHz, DMSO-d_6) δ_c = 54.3, 59.5, 112.1, 118.3, 128.6, 129.7, 130.6, 131.3, 132.4, 136.7, 138.3, 148.1, 159.9, 168.8, 169.3, 194.5; Anal. Calcd. for $C_{16}H_{10}Cl_2N_2O_4$: C, 52.72; H, 2.80; N, 7.69. Found: C, 52.63; H, 2.76; N, 7.67. Compound **4e**: Colorless crystals; m.p = 220–223 °C; IR (KBr, ν, Cm^{-1}): 3425 and 3325 (NH_2), 3463 (OH), 2214 (CN), 1642 (C = O) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ = 4.12 (dd, 1H, ^2J = 15.2, ^4J = 5.2 Hz, CH_{aliph}), 4.23 (dd, 1H, ^2J = 15.2, ^4J = 5.2 Hz, CH_{aliph}), 4.88 (t, 1H, ^4J = 5.2 Hz, OH), 5.64 (s, 1H, CH_{vinyl}), 6.35 (s, 1H, CH_{aliph}), 7.11–7.21 (m, 2H, CH_{arom}), 7.30 (s, 2H, NH_2), 7.40–7.80 (m, 2H, CH_{arom}); ^{13}C NMR (100 MHz, DMSO-d_6) δ_c = 55.2, 59.2, 111.4, 114.7 (d, ^2J = 12.0 Hz, C–F), 114.8 (d, ^2J = 20.0 Hz, C–F), 119.1, 123.8 (d, ^4J = 2.0 Hz, C–F), 130.3 (d, ^3J = 8.0 Hz, C–F), 136.4, 143.2 (d, ^3J = 7.0 Hz, C–F), 159.3, 162.1 (d, ^1J = 264.0 Hz, C–F), 168.2, 169.5, 195.9; Anal. Calcd. for $C_{16}H_{11}FN_2O_4$: C, 61.23; H, 3.59; N, 8.94. Found: C, 61.15; H, 3.53; N, 8.91. Compound **4f**: Colorless crystals; m.p = 219–221 °C; IR (KBr, ν, Cm^{-1}): 3350 and 3366 (NH_2), 3345 (OH), 2221 (CN), 1462 (C=O) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ = 2.31 (s, 3 H, CH_3), 4.11 (dd, 1H, ^2J = 15.6, ^4J = 6.4 Hz, CH_{aliph}), 4.25 (dd, 1H, ^2J = 15.6, ^4J = 6.4 Hz, CH_{aliph}), 4.73 (t, 1H, ^4J = 6.4 Hz, OH), 5.69 (s, 1H, CH_{vinyl}), 6.34 (s, 1H, CH_{aliph}), 6.72 (d, 1H, ^3J = 7.6 Hz, CH_{arom}), 7.12 (d, 1H, ^3J = 7.6 Hz, CH_{arom}), 7.08 (s, 2H, NH_2), 7.28 (t, 1H, ^3J = 7.2 Hz, CH_{arom}); ^{13}C NMR (100 MHz, DMSO-d_6) δ_c = 20.9, 55.7, 59.0, 111.3, 119.3, 124.9, 128.1, 128.7, 136.3, 138.2, 140.8, 149.1, 159.1, 168.2, 169.6, 195.4; Anal. Calcd. for $C_{17}H_{14}N_2O_4$: C, 65.01; H, 4.16; N, 9.05. Found: C, 65.80; H, 4.55; N, 9.03. Compound **4g**: Colorless crystals; m.p = 242–244 °C; IR (KBr, ν, Cm^{-1}): 3431 and 3325 (NH_2), 3443 (OH), 2207 (CN), 1639 (C=O) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ = 4.15 (dd, 1H, ^2J = 15.1, ^4J = 6.0 Hz, CH_{aliph}), 4.23 (dd, 1H, ^2J = 15.1, ^4J = 6.0 Hz, CH_{aliph}), 5.88 (t, 1H, ^4J = 6.0 Hz, OH), 5.69 (s, 1H, CH_{vinyl}), 6.34 (s, 1H, CH_{aliph}), 7.31 (s, 2H, NH_2), 7.35–7.60 (m, 4H, CH_{arom}); ^{13}C NMR (100 MHz, DMSO-d_6) δ_c = 55.1, 59.1, 114.2, 119.2, 122.1, 127.2, 130.6, 130.8, 131.5, 136.2, 143.3, 143.8, 159.2, 168.2, 169.3, 195.9; Anal. Calcd. for $C_{16}H_{11}BrN_2O_4$: C, 51.33; H, 2.99; N, 7.48. Found: C, 51.22; H, 2.96; N, 7.47. Compound **4h**: Colorless crystals; m.p = 271–273 °C; IR (KBr, ν, Cm^{-1}): 3434 and 3320 (NH_2), 3442 (OH), 2116 (CN), 1640 (C=O) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ = 3.73 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 4.17 (dd, 1H, ^2J = 15.1, ^4J = 4.8 Hz, CH_{aliph}), 4.22 (dd, 1H, ^2J = 15.1, ^4J = 4.8 Hz, CH_{aliph}), 7.72 (t, 1H, ^4J = 4.8 Hz, OH), 5.70 (s, 1H, CH_{vinyl}), 6.33 (d, 2H, ^4J = 2.0 Hz, CH_{arom}), 6.42 (s, 1H, CH_{aliph}), 6.46 (d, 2H, ^4J = 2.0 Hz, CH_{arom}), 7.23 (s, 2H, NH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ_c = 55.2, 55.3, 59.1, 99.1, 105.8, 111.3, 119.1, 136.4, 143.3, 148.7, 159.3, 160.7, 168.3, 169.5, 195.6; Anal. Calcd. for $C_{18}H_{16}N_2O_6$: C, 60.77; H, 4.59; N, 7.88. Found: C, 60.67; H, 4.53; N, 7.86. Compound **4i**: Colorless crystals; m.p = 248–250 °C; IR (KBr, ν, Cm^{-1}): 3466 and 3352 (NH_2), 3551 (OH), 2195 (CN), 1633 (C=O) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ = 4.15 (dd, 1H, ^2J = 15.3, ^4J = 6.0 Hz, CH_{aliph}), 4.23 (dd, 1H, ^2J = 15.3, ^4J = 6.0 Hz, CH_{aliph}), 4.85 (t, 1H, ^4J = 6.0 Hz, OH), 5.71 (s, 1H, CH_{vinyl}), 6.34 (s, 1H, CH_{aliph}), 7.18–7.25 (m, 2H, CH_{arom}), 7.27 (s, 2H, NH_2), 7.32–7.40 (m, 2H, CH_{arom}); ^{13}C NMR (100 MHz, DMSO-d_6) δ_c = 55.5, 59.1, 111.5, 115.6 (d, ^2J = 21.0 Hz, C–F), 119.2, 129.8 (d, ^3J = 9.0 Hz, C–F), 136.3, 136.9 (d, ^4J = 3.0 Hz, C–F), 148.7, 159.9, 161.9 (d, ^1J = 295.0 Hz, C–F), 168.2, 169.3, 198.7; Anal. Calcd. for $C_{16}H_{11}FN_2O_4$: C, 61.26; H, 3.59; N, 8.93. Found: C, 61.15; H, 3.53; N, 8.91. Compound **4j**: Colorless crystals; m.p = 251–253 °C; IR (KBr, ν, Cm^{-1}): 3313 and 3199 (NH_2), 3369 (OH), 2198 (CN), 1629 (C=O) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ = 4.15 (dd, 1H, ^2J = 15.0, ^4J = 6.4 Hz, CH_{aliph}), 4.42 (dd, 1H, ^2J = 15.0, ^4J = 6.4 Hz, CH_{aliph}), 4.95 (t, 1H, ^4J = 6.4 Hz, OH), 5.70 (s, 1H, CH_{vinyl}), 6.35 (s, 1H, CH_{aliph}), 7.34 (s, 2H, NH_2), 7.43 (dd, 1H, ^3J = 7.6, ^4J = 4.8 Hz, CH_{arom}), 7.41 (dt, 1H, ^3J = 7.6, ^4J = 6.0 Hz, CH_{arom}), 8.52–8.58 (m, 2H, CH_{arom}); ^{13}C NMR (100 MHz, DMSO-d_6) δ_c = 54.7, 59.4, 111.6, 119.1, 124.2, 145.5, 136.2, 136.4, 141.9, 149.0, 149.2, 159.3, 168.3, 169.6, 195.7; Anal. Calcd. for $C_{15}H_{11}N_3O_4$: C, 60.76; H, 3.78; N, 14.16. Found: C, 60.61; H, 3.73; N, 14.14. Compound **4k**: Colorless crystals; m.p = 233–235 °C; IR (KBr, ν, Cm^{-1}): 3377 and 3171 (NH_2), 3351 (OH), 2119 (CN), 1640 (C=O) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ = 4.13 (dd, 1H, ^2J = 15.2, ^4J = 5.6 Hz, CH_{aliph}), 4.25 (dd, 1H, ^2J = 15.2, ^4J = 5.6 Hz, CH_{aliph}), 4.91 (t, 1H, ^4J = 5.6 Hz, OH), 5.71 (s, 1H, CH_{vinyl}), 6.36 (s, 1H, CH_{aliph}), 7.35 (d, 2H, ^3J = 5.6, CH_{arom}),7.38 (s, 2H, NH_2), 8.59 (d, 2H, ^3J = 5.6, CH_{arom}); ^{13}C NMR (100 MHz, DMSO-d_6) δ_c = 54.3, 59.1, 111.5, 118.6, 122.9, 136.6, 136.4, 147.5, 149.1, 150.2, 159.4, 168.3, 169.5, 195.8; Anal. Calcd. for $C_{15}H_{11}N_3O_4$: C, 60.69; H, 3.78; N, 14.16. Found: C, 60.61; H, 3.73; N, 14.14. Compound **4l**: Colorless crystals; m.p = 223–225 °C; IR (KBr, ν, Cm^{-1}): 3317 and 3191 (NH_2), 3368 (OH), 2189 (CN), 1629 (C=O) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ = 4.16 (dd, 1H, ^2J = 15.3, ^4J = 6.1 Hz, CH_{aliph}), 4.19 (dd, 1H, ^2J = 15.3, ^4J = 6.1 Hz, CH_{aliph}), 4.95 (t, 1H, ^4J = 6.1 Hz, OH), 5.23 (s, 1H, CH_{vinyl}), 6.35 (s, 1H, CH_{aliph}), 7.08 (s, 2H, NH_2), 7.46 (d, 2H, ^3J = 4.1, CH_{arom}), 7.50–7.55 (m, 2H, CH_{arom}); ^{13}C NMR (100 MHz, DMSO-d_6) δ_c = 33.4, 55.3, 59.1, 106.5, 110.6, 111.9, 112.6, 119.4, 142.5, 142.1, 152.2, 159.4, 168.7, 196.6; Anal. Calcd. for $C_{14}H_{10}N_2O_5$: C, 58.83; H, 3.57; N, 9.81. Found: C, 58.74; H, 3.52; N, 9.79. Compound **4m**: Colorless crystals; m.p = 235–237 °C; IR (KBr, ν, Cm^{-1}): 3182 and 3191 (NH_2), 3361 (OH), 2110 (CN), 1631 (C=O) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ = 4.18 (dd, 1H, ^2J = 15.6, ^4J = 5.9 Hz, CH_{aliph}), 4.25 (dd, 1H, ^2J = 15.5, ^4J = 5.9 Hz, CH_{aliph}), 4.96 (t, 1H, ^4J = 5.9 Hz, OH), 5.29 (s, 1H, CH_{vinyl}), 6.34 (s, 1H, CH_{aliph}), 6.98 (s, 2H, NH_2), 7.39 (d, 2H, ^3J = 4.7, CH_{arom}), 7.45–7.60 (m, 2H, CH_{arom}); ^{13}C NMR (100 MHz, DMSO-d_6) δ_c = 32.9, 58.3, 58.9, 111.5, 112.6, 119.5, 123.6, 119.4, 127.5, 139.4, 142.5, 159.4, 169.2, 197.2; Anal. Calcd. for $C_{14}H_{10}N_2O_4S$: C, 55.70; H, 3.36; N, 9.29. Found: C, 55.62; H, 3.33; N, 9.27.