Research Article

Ultrasound Promoted Green and Facile One-Pot Multicomponent Synthesis of 3,4-dihydropyrano[c]Chromene Derivatives

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Ultrasound promoted mild one-pot multicomponent synthesis of 3,4-dihydropyrano[c]chromenes from 4-hydroxycoumarin, arylaldehydes and malononitrile was achieved in aqueous media. The methodology promises advantages of short reaction times, environmentally benign conditions, high yields, and operational convenience.

1. Introduction

Dihydropyrano[c]chromene scaffold constitutes an important structural component in several naturally occurring and synthetic molecules displaying broad spectrum of biological activities [1, 2] such as antibacterial [3], antineoplastic activity [4], antimicrobial activity [5], and anti-HIV activity [6]. Their biological efficacy is further demonstrated from their applications as cognitive enhancers for the treatment of neurodegenerative Alzheimer's disease [7]. Consequently, numerous elegant synthetic methodologies have been developed for the synthesis of these heterocycles in recent times. Shaker has reported the synthesis of dihydropyrano[c]chromenes in the presence of organic bases like piperidine/pyridine in ethanol [8], Kidwai documented that microwave irradiation promoted the potassium carbonate catalyzed synthesis [9] of the pyranochromenes while Abdolmohammadi and Saxena et al. have reported diammonium hydrogen phosphate catalyzed synthesis in aqueous ethanol [10]. Shaabani et al. and Shaterian and Oveisi have presented their synthesis in ionic liquids 1,1,3,3-N,N,N',N'-tetramethylguanidinium trifluoroacetate (TMGT) and 3-Hydroxypropanaminium Acetate (HPAA), respectively, [11, 12].

Green chemistry in recent times has gained immense attention and played a significant role in revolutionizing

synthetic organic chemistry to minimize the usage of organic solvents and their disposal thereby developing environment-friendly organic synthesis [13]. In this context, water has been explored in several synthetic methodologies as an efficient solvent which successfully displaced the usage of harmful organic solvents thereby reducing the generation of hazardous wastes [14]. On the other hand, ultrasound promoted reactions paved way for the modification and improvement of several existing synthetic methodologies by enhancing their reaction rates [15, 16] thus appending considerable value addition to the green chemistry procedures. The cavitation energy produced during the process of ultrasonication paves way for alternative pathways due to the formation of high energy intermediates thereby modifying and improving the reaction rates [17].

2. Results and Discussion

Earlier, we have reported ultrasound promoted asymmetric Mannich reaction and chromeno-quinolines synthesis [18, 19]. In continuation of our efforts to develop green chemistry protocols and foreseeing the importance of 3,4-dihydropyrano[c]chromenes synthesis, we have developed a mild and efficient procedure for their synthesis under

SCHEME 1: Synthetic route for the synthesis of 3,4-dihydropyrano[c]chromene derivatives **4a–4p**. Reagents and conditions: Sodium acetate (30 mol%), H₂O, Ultrasound irradiation, and room temperature.

TABLE 1: Optimization of reaction conditions with different solvents and catalysts for the synthesis of **4a**^a.

Entry	Catalyst	Solvent	Mol (%)	Time (min)	Yield (%) ^b
1	Trisodium citrate	H ₂ O	30	10	57
2	NH ₄ OAc	H ₂ O	30	10	70
3	L-proline	H ₂ O	30	10	30
4	Nafion-H	H ₂ O	50 mg	10	40
5	Amberlyst	H ₂ O	50 mg	10	30
6	Sodium acetate	H ₂ O	30	10	92
7	Sodium acetate	PEG	30	10	50
8	Sodium acetate	DMSO	30	10	36
9	Sodium acetate	DMF	30	10	28
10	Sodium acetate	EtOH	30	10	70
11	Sodium acetate	H ₂ O	30	180	30 ^c
12	—	H ₂ O	—	30	35 ^d

^aThe reactions were carried out at room temperature using 4-hydroxycoumarin (1 mmol), benzaldehyde (1 mmol), malononitrile (1.2 mmol), and catalyst (30 mol%) in water (5 mL) under ultrasound conditions, ^bYields refer to the precipitated products, ^cabsence of ultrasound conditions, ^dOnly ultrasound, no catalyst.

ultrasound conditions using sodium acetate as a catalyst in aqueous conditions at room temperature (Scheme 1).

In order to optimize the reaction conditions, the synthesis of 2-amino-5-oxo-4-phenyl-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile (**4a**) from the condensation of 4-hydroxycoumarin, benzaldehyde, and malononitrile was studied in the presence of a variety of catalysts and solvents under ultrasound conditions. As shown in Table 1, ultrasonication promotes the formation of products with varying yields and reaction rates under different catalytic systems. First, a trial reaction was performed in water with 30 mol% of trisodium citrate (Na₃C₆H₅O₇) as a promoter (Table 1, entry 1). It was observed that after 10 minutes of the ultrasound irradiation the required product was obtained in 57% yield. Among various other catalysts screened ammonium acetate, L-proline, Nafion-H, and Amberlyst afforded poor-to-moderate yields (30–70%), while sodium acetate (NaOAc) gave 92% yield of the desired product (Table 1, entry 2–6) in just 10 minutes. To validate the choice of solvent, various solvents were screened to check their influence on the rates and yields of the reaction (Table 1, entries 7–10). Solvents such as PEG, DMSO, and DMF afforded poor-to-moderate yields (28–50%), while better yields of the products were observed when the reaction was conducted in ethanol (70%). Further to authenticate the effect of ultrasound conditions, a reaction was conducted in absence of ultrasound which resulted in only 30% of desired product after stirring for

3 hours (Table 1, Entry 11). Surprisingly, ultrasonication alone in absence of catalyst was able to promote the reaction affording the product in 35% yield after of 30 minutes (Table 1, Entry 12). The best yield was obtained when the reaction was performed with sodium acetate as a catalyst in water under ultrasonication conditions.

With the above optimized reaction conditions, a series of 3,4-dihydropyrano[c]chromene derivatives **4a–4p** were synthesized (Table 2). As shown in Table 2, when halogen substituted aromatic aldehydes such as 2-chloro, 3-chloro, 2,4-dichloro, 2,3-dichloro, 4-chloro, 4-bromo, and 4-fluoro substrates were employed under the reaction conditions excellent yields (82–94%) of the corresponding products **4b–4h** were obtained (Table 2, entries 2–8). Aromatic aldehydes possessing electron donating substituents such as 2-methyl, 4-methyl, 4-methoxy, 3,4-dimethoxy, and 2,5-dimethoxy have afforded the pyranochromenes **4i–4m** in 76–92% yields (Table 2, entries 9–13). Similarly, electron withdrawing aromatic aldehydes possessing 3-nitro and 4-nitro groups also afforded the pyranochromene derivatives **4n–4o** in 85% and 94% yields, respectively, (Table 2, entries 14 and 15). Finally, p-hydroxybenzaldehyde possessing phenol group also afforded the required product **4p** in 91% yield (Table 2, entry 16). All the above reactions were time optimized and products were obtained as precipitates from the reaction mixtures in pure form which evaded the tedious column purification procedures. From the above observations it is

TABLE 2: Ultrasound promoted synthesis of 3,4-Dihydropyrano[*c*]chromenes **4a–4p** using NaOAc as a catalyst^a.

Entry	Ar ^b	Product	Time (min)	Yield (%) ^c	Melting point (°C)/(lit.)
1		4a	10	92	256–259/(258–260) [8]
2		4b	8	85	264–266/(266–268) [20]
3		4c	6	82	246–248/(245–247) [21]
4		4d	5	86	255–257/(257–259) [10]
5		4e	6	76	282–284/(280–282) [10]
6		4f	5	94	256–258/(258–260) [8]
7		4g	7	82	247–249/(249–251) [22]

TABLE 2: Continued.

Entry	Ar ^b	Product	Time (min)	Yield (%) ^c	Melting point (°C)/(lit.)
8		4h	5	90	262–264/(260–262) [20]
9		4i	6	88	258–260/(260–262) [23]
10		4j	8	76	251–253/(250–252) [21]
11		4k	10	92	238–240/(232–234) [8]
12		4l	10	90	226–228/(228–230) [21]
13		4m	8	90	246–248/(247–248) [11]
14		4n	7	85	258–260/(262–264) [10]

TABLE 2: Continued.

Entry	Ar ^b	Product	Time (min)	Yield (%) ^c	Melting point (°C)/(lit.)
15		4o	5	94	258–260/(255–256) [10]
16		4p	10	91	259–260/(261–262) [24]
17		4a	20	88	256–259/(258–260) ^d

^a Reactions were carried out at room temperature for 5–10 minutes using 4-hydroxycoumarin (1 mmol), aromatic aldehydes (1 mmol), malononitrile (1.2 mmol), and sodium acetate (30 mol%) in water (5 mL) under ultrasound conditions, ^bAr: aromatic group as shown in Scheme 1, ^cyields refer to the precipitated products, ^dScale-up experiment was conducted on 5 g batch for the synthesis of **4a**.

evident that the ultrasound promoted protocol has successfully accommodated wide range of aromatic aldehydes possessing broad array of functional groups and substitution patterns.

To further explore the efficacy of ultrasound methodology on the present methodology a scale-up experiment was conducted on 5g batch for the synthesis of **4a**. Gratifyingly, we observed that the ultrasound methodology provides 88% of **4a** (Table 2, entry 17) as a pure precipitate with a slight compromise in time (20 minutes).

3. Conclusion

In conclusion, we have developed a simple, efficient, and green protocol for the synthesis of 3,4-dihydro-pyrano[c]chromenes in high yields promoted by ultrasound conditions in aqueous medium. The results also suggest that the present methodology can be effectively applied for the synthesis of the products in grams scale. Finally, the operationally simple protocol did not require any column purifications as the products were isolated as pure precipitates from the reaction mixture.

4. Experimental

All reagents were purchased from Merck and Avra synthesis Pvt. Ltd. and used without further purification. All yields refer to the precipitated products. All the products were

characterized by ¹H NMR, ¹³C NMR, IR, and EI-Mass analysis and were found to be in good agreement with those reported in the literature. The ¹H NMR (500 MHz) and ¹³C NMR (125 MHz) were recorded on a Bruker Avance DPX 500 MHz instrument at room temperature in DMSO using TMS as an internal reference. IR spectra were recorded on a Bruker α alpha-T spectrophotometer. Melting points were determined by NETZSCH DSC 200 instrument. Sonication was performed in Leelasonic ultrasonic reactor with a frequency of 40 KHz and a nominal power of 250 W.

4.1. General Procedure for the Synthesis of Dihydropyrano[c]chromene Derivatives 4a–p. A solution of 4-hydroxycoumarin **1** (1 mmol), aromatic aldehydes **2a–p** (1 mmol), malononitrile **3** (1.2 mmol), and sodium acetate (30 mol %) in H₂O was sonicated at room temperature for required time (Table 2). After completion of the reaction as monitored by TLC the precipitate obtained was filtered and washed with aqueous ethanol to give pure products. All the obtained products were characterized by comparing their physical data with the authentic samples.

2-Amino-5-oxo-4-phenyl-4,5-dihydropyrano[3,2-c] chromene-3-carbonitrile 4a. M.p. 256–259°C [lit: 258–260°C] [8]. ¹H NMR (500 MHz, DMSO-d₆): δ 4.36 (1H, s, CH), 7.23 (2H, d, J = 7.8 Hz, H_{Ar}), 7.29 (1H, br s, H_{Ar}), 7.33

(2H, t, $J = 7.5$ Hz, H_{Ar}), 7.32 (2H, br s, NH_2), 7.45 (1H, d, $J = 8.4$ Hz, H_{Ar}), 7.49 (1H, t, $J = 7.6$ Hz, H_{Ar}), 7.71 (1H, t, $J = 7.5$ Hz, H_{Ar}), 7.91 (1H, d, $J = 7.8$ Hz, H_{Ar}) ppm. ^{13}C NMR (125 MHz, DMSO- d_6): δ 58.18, 104.88, 114.84, 117.44, 121.10, 123.34, 125.64, 127.99, 128.50, 129.59, 132.79, 145.21, 153.56, 154.79, 158.86, 161.41 ppm. IR (KBr, cm^{-1}): 3378, 3286, 3178, 2196, 1709, 1674, 1604. EI-MS: $m/z = 316.06$.

2-Amino-4-(2-chlorophenyl)-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile 4b. M.p. 264–266°C [lit: 266–268°C] [20]. 1H NMR (500 MHz, DMSO- d_6): δ 4.48 (1H, s, CH), 7.15 (1H, d, $J = 7.8$ Hz, H_{Ar}), 7.54 (1H, d, $J = 7.8$ Hz, H_{Ar}), 7.22 (2H, t, $J = 7.5$ Hz, H_{Ar}), 7.25 (2H, br s, NH_2), 7.42 (1H, d, $J = 8.4$ Hz, H_{Ar}), 7.55 (1H, t, $J = 7.6$ Hz, H_{Ar}), 7.61 (1H, t, $J = 7.5$ Hz, H_{Ar}), 7.89 (1H, d, $J = 7.8$ Hz, H_{Ar}) ppm. ^{13}C NMR (125 MHz, DMSO- d_6): δ 57.65, 105.40, 112.80, 118.34, 119.64, 122.38, 126.42, 128.38, 131.75, 132.85, 135.75, 143.12, 152.06, 155.62, 157.73, 161.54 ppm. IR (KBr, cm^{-1}): 3374, 3283, 3175, 2192, 1710, 1672, 1605. EI-MS: $m/z = 350.04$.

2-Amino-4-(3-chlorophenyl)-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile 4c. M.p. 246–248°C [lit: 245–247°C] [21]. 1H NMR (500 MHz, DMSO- d_6): δ 4.54 (1H, s, CH), 7.34 (1H, d, $J = 6.7$ Hz, H_{Ar}), 7.41 (1H, t, $J = 7.6$ Hz, H_{Ar}), 7.66 (2H, br s, NH_2), 7.74 (1H, t, $J = 7.6$ Hz, H_{Ar}), 7.54 (1H, dt, $J = 7.5, 1.3$ Hz, H_{Ar}), 7.68 (1H, d, $J = 6.8$ Hz, H_{Ar}), 7.89 (1H, dd, $J = 6.8, 1.2$ Hz, H_{Ar}), 8.12 (1H, dd, $J = 8.4, 1.4$ Hz, H_{Ar}), 8.14 (1H, s, H_{Ar}) ppm. ^{13}C NMR (125 MHz, DMSO- d_6): δ 58.62, 104.74, 113.81, 117.32, 119.73, 121.13, 123.24, 123.64, 125.67, 131.92, 134.24, 135.63, 145.36, 147.62, 152.43, 154.65, 159.03, 160.46 ppm. IR (KBr, cm^{-1}): 3404, 3322, 3183, 2198, 1706, 1674, 1531, 1349. EI-MS: $m/z = 350.05$.

2-Amino-4-(2,4-dichlorophenyl)-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile 4d. M.p. 255–257°C [lit: 257–259°C] [10]. 1H NMR (500 MHz, DMSO- d_6): δ 4.99 (1H, s, CH), 7.36 (1H, dd, $J = 8.3, 1.9$ Hz, H_{Ar}), 7.40 (1H, d, $J = 8.3$ Hz, H_{Ar}), 7.41 (2H, br s, NH_2), 7.46 (1H, d, $J = 8.3$ Hz, H_{Ar}), 7.51 (1H, t, $J = 7.7$ Hz, H_{Ar}), 7.56 (1H, d, $J = 2.1$ Hz, H_{Ar}), 7.73 (1H, t, $J = 8.2$ Hz, H_{Ar}), 7.92 (1H, d, $J = 8.9$ Hz, H_{Ar}) ppm. ^{13}C NMR (125 MHz, DMSO- d_6): δ 57.10, 103.38, 113.71, 117.47, 119.43, 123.42, 125.57, 128.71, 129.73, 132.95, 133.28, 133.96, 134.28, 140.26, 153.14, 155.05, 159.05, 160.23 ppm. IR (KBr, cm^{-1}): 3463, 3295, 3163, 3070, 2198, 1715, 1674, 1590. EI-MS: $m/z = 384.02$.

2-Amino-4-(2,3-dichlorophenyl)-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile 4e. M.p. 282–284°C [lit: 280–282°C] [10]. 1H NMR (500 MHz, DMSO- d_6): δ 4.86 (1H, s, CH), 7.36 (1H, dd, $J = 8.3, 1.9$ Hz, H_{Ar}), 7.40 (1H, d, $J = 8.3$ Hz, H_{Ar}), 7.41 (2H, br s, NH_2), 7.46 (1H, d, $J = 8.3$ Hz, H_{Ar}), 7.51 (1H, t, $J = 7.7$ Hz, H_{Ar}), 7.56 (1H, d, $J = 2.1$ Hz, H_{Ar}), 7.73 (1H, t, $J = 8.2$ Hz, H_{Ar}), 7.92 (1H, d, $J = 8.9$ Hz, H_{Ar}) ppm. ^{13}C NMR (125 MHz, DMSO- d_6): δ 57.10, 103.38, 113.71, 117.47, 119.43, 123.42, 125.57, 128.71,

129.73, 132.95, 133.28, 133.96, 134.28, 140.26, 153.14, 155.05, 159.05, 160.23 ppm. IR (KBr, cm^{-1}): 3463, 3295, 3163, 3070, 2198, 1715, 1674, 1590. EI-MS: $m/z = 384.02$.

2-Amino-4-(4-chlorophenyl)-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile 4f. M.p. 256–258°C [lit: 258–260°C] [8]. 1H NMR (500 MHz, DMSO- d_6): δ 4.50 (1H, s, CH), 7.32 (2H, d, $J = 8.2$ Hz, H_{Ar}), 7.26 (2H, br s, NH_2), 7.34 (2H, br s, H_{Ar}), 7.34 (1H, d, $J = 8.2$ Hz, H_{Ar}), 7.58 (1H, t, $J = 7.6$ Hz, H_{Ar}), 7.78 (1H, t, $J = 7.8$ Hz, H_{Ar}), 7.92 (1H, d, $J = 7.8$ Hz, H_{Ar}) ppm. ^{13}C NMR (125 MHz, DMSO- d_6): δ 58.65, 104.40, 113.80, 117.34, 119.86, 123.38, 125.42, 129.28, 130.45, 132.65, 133.75, 143.12, 153.06, 154.42, 158.93, 160.34 ppm. IR (KBr, cm^{-1}): 3380, 3318, 3179, 2194, 1715, 1665, 1605. EI-MS: $m/z = 350.05$.

2-Amino-4-(4-bromophenyl)-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile 4g. M.p. 247–249°C [lit: 249–251°C] [22]. 1H NMR (500 MHz, DMSO- d_6): δ 4.42 (1H, s, CH), 7.35 (2H, d, $J = 8.2$ Hz, H_{Ar}), 7.28 (2H, br s, NH_2), 7.42 (2H, br s, H_{Ar}), 7.38 (1H, d, $J = 8.2$ Hz, H_{Ar}), 7.62 (1H, t, $J = 7.6$ Hz, H_{Ar}), 7.88 (1H, t, $J = 7.8$ Hz, H_{Ar}), 7.98 (1H, d, $J = 7.8$ Hz, H_{Ar}) ppm. ^{13}C NMR (125 MHz, DMSO- d_6): δ 57.45, 102.50, 113.78, 116.54, 118.76, 122.68, 124.42, 129.68, 131.54, 133.45, 134.85, 144.42, 154.76, 155.62, 159.32, 160.34 ppm. IR (KBr, cm^{-1}): 3380, 3318, 3179, 2194, 1715, 1665, 1605. EI-MS: $m/z = 394.01$.

2-Amino-4-(4-fluorophenyl)-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile 4h. M.p. 262–264°C [lit: 260–262°C] [20]. 1H NMR (500 MHz, DMSO- d_6): δ 4.47 (1H, s, CH), 7.45 (2H, d, $J = 8.2$ Hz, H_{Ar}), 7.38 (2H, br s, NH_2), 7.54 (2H, br s, H_{Ar}), 7.46 (1H, d, $J = 8.2$ Hz, H_{Ar}), 7.72 (1H, t, $J = 7.6$ Hz, H_{Ar}), 7.82 (1H, t, $J = 7.8$ Hz, H_{Ar}), 7.96 (1H, d, $J = 7.8$ Hz, H_{Ar}) ppm. ^{13}C NMR (125 MHz, DMSO- d_6): δ 56.24, 105.40, 114.80, 118.34, 119.86, 124.38, 125.42, 129.76, 131.25, 132.98, 135.75, 144.12, 153.56, 154.82, 157.93, 161.34 ppm. IR (KBr, cm^{-1}): 3378, 3294, 2192, 1714, 1679, 1605, 1507, 1378. EI-MS: $m/z = 334.06$.

2-Amino-5-oxo-4-o-tolyl-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile 4i. M.p. 258–260°C [lit: 260–262°C] [23]. 1H NMR (500 MHz, DMSO- d_6): δ 2.36 (3H, s, CH_3), 4.28 (1H, s, CH), 7.16 (1H, d, $J = 7.8$ Hz, H_{Ar}), 7.64 (1H, d, $J = 7.8$ Hz, H_{Ar}), 7.32 (2H, t, $J = 7.5$ Hz, H_{Ar}), 7.38 (2H, br s, NH_2), 7.46 (1H, d, $J = 8.4$ Hz, H_{Ar}), 7.58 (1H, t, $J = 7.6$ Hz, H_{Ar}), 7.68 (1H, t, $J = 7.5$ Hz, H_{Ar}), 7.78 (1H, d, $J = 7.8$ Hz, H_{Ar}) ppm. ^{13}C NMR (125 MHz, DMSO- d_6): δ 56.95, 107.40, 116.80, 118.34, 119.34, 124.38, 127.42, 128.38, 131.65, 134.85, 135.75, 146.12, 153.06, 155.62, 157.73, 162.54 ppm. IR (KBr, cm^{-1}): 3378, 3284, 3176, 2194, 1710, 1672, 1605. EI-MS: $m/z = 330.09$.

2-Amino-5-oxo-4-p-tolyl-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile 4j. (Table 2 entry 10). M.p. 251–253°C [lit: 250–252°C] [21]. 1H NMR (500 MHz, DMSO- d_6): δ 2.38 (3H, s, CH_3), 4.38 (1H, s, CH), 7.34 (2H, d, $J = 8.2$ Hz, H_{Ar}), 7.45 (2H, br s, NH_2), 7.38 (2H, br s, H_{Ar}), 7.34 (1H, d, $J = 8.2$ Hz, H_{Ar}), 7.58 (1H, t, $J = 7.6$ Hz, H_{Ar}), 7.78 (1H, t, $J = 7.8$ Hz,

H_{Ar}), 7.82 (1H, d, $J = 7.8$ Hz, H_{Ar}) ppm. ^{13}C NMR (125 MHz, DMSO- d_6): δ 59.65, 103.40, 115.80, 118.34, 119.86, 122.38, 125.42, 129.28, 130.45, 131.65, 133.75, 144.12, 153.06, 154.42, 158.93, 160.34 ppm. IR (KBr, cm^{-1}): 3378, 3296, 2192, 1710, 1676, 1604, 1510, 1378. EI-MS: $m/z = 330.10$.

2-Amino-4-(4-methoxyphenyl)-5-oxo-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile 4k. M.p. 238–240°C [lit: 232–234°C] [8]. ^1H NMR (500 MHz, DMSO- d_6): δ 3.72 (3H, s, OCH_3), 4.40 (1H, s, CH), 6.87 (2H, d, $J = 8.1$ Hz, H_{Ar}), 7.18 (2H, d, $J = 8.1$ Hz, H_{Ar}), 7.37 (2H, br s, NH_2), 7.45 (1H, d, $J = 8.3$ Hz, H_{Ar}), 7.49 (1H, t, $J = 7.8$ Hz, H_{Ar}), 7.70 (1H, t, $J = 7.7$ Hz, H_{Ar}), 7.89 (1H, d, $J = 7.7$ Hz, H_{Ar}) ppm. ^{13}C NMR (125 MHz, DMSO- d_6): δ 55.90, 59.10, 105.13, 113.84, 114.71, 117.37, 120.18, 123.29, 125.47, 129.64, 133.66, 136.26, 152.94, 153.94, 158.79, 159.20, 160.38 ppm. IR (KBr, cm^{-1}): 3378, 3314, 3190, 2196, 1709, 1672, 1608. EI-MS: $m/z = 346.30$.

2-Amino-4-(3,4-dimethoxyphenyl)-5-oxo-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile 4l. M.p. 226–228°C [lit: 228–230°C] [21]. ^1H NMR (500 MHz, DMSO- d_6): δ 3.70 (6H, s, 2OCH_3), 4.40 (1H, s, CH), 6.75 (1H, d, $J = 8.15$ Hz, H_{Ar}), 6.86 (2H, d, $J = 8$ Hz, H_{Ar}), 7.31 (2H, br s, NH_2), 7.38 (1H, d, $J = 8.25$ Hz, H_{Ar}), 7.43 (1H, t, $J = 7.5$ Hz, H_{Ar}), 7.64 (1H, t, $J = 7.65$ Hz, H_{Ar}), 7.88 (1H, d, $J = 7.65$ Hz, H_{Ar}) ppm. ^{13}C NMR (125 MHz, DMSO- d_6): δ 36.51, 55.50, 55.56, 58.27, 104.08, 111.78, 111.96, 112.97, 116.40, 119.22, 119.67, 122.38, 124.47, 132.68, 135.82, 148.02, 148.58, 152.05, 153.11, 157.93, 159.49 ppm. IR (KBr, cm^{-1}): 3406, 3326, 2196, 1710, 1672, 1609, 1517, 1378. EI-MS: $m/z = 376.11$.

2-Amino-4-(2,5-dimethoxyphenyl)-5-oxo-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile 4m. M.p. 246–248°C [lit: 247–248°C] [11]. ^1H NMR (500 MHz, DMSO- d_6): δ 3.63 (3H, s, OCH_3), 3.64 (3H, s, OCH_3), 4.64 (1H, s, CH), 6.66 (1H, d, $J = 2.3$ Hz, H_{Ar}), 6.75–6.79 (1H, m, H_{Ar}), 6.90 (1H, d, $J = 8.8$ Hz, H_{Ar}), 7.25 (2H, s, NH_2), 7.41–7.49 (2H, m, H_{Ar}), 7.67 (1H, t, $J = 7.7$ Hz, H_{Ar}), 7.89 (d, $J = 7.7$ Hz, 1H, H_{Ar}) ppm. ^{13}C NMR (125 MHz, DMSO- d_6): δ 32.6, 55.2, 56.4, 56.8, 103.1, 112.2, 112.9, 113.1, 115.7, 116.4, 119.2, 122.2, 124.5, 131.9, 132.6, 151.5, 152.0, 153.1, 153.9, 158.5, 159.4 ppm. IR (KBr, cm^{-1}): 3403, 3322, 3192, 2195, 1708, 1672, 1605, 1501, 1380. EI-MS: $m/z = 376.11$.

2-Amino-4-(3-nitrophenyl)-5-oxo-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile 4n. M.p. 258–260°C [lit: 262–264°C] [10]. ^1H NMR (500 MHz, DMSO- d_6): δ 4.64 (1H, s, CH), 7.38 (1H, d, $J = 6.7$ Hz, H_{Ar}), 7.42 (1H, t, $J = 7.6$ Hz, H_{Ar}), 7.68 (2H, br s, NH_2), 7.76 (1H, t, $J = 7.6$ Hz, H_{Ar}), 7.45 (1H, dt, $J = 7.5, 1.3$ Hz, H_{Ar}), 7.76 (1H, d, $J = 6.8$ Hz, H_{Ar}), 7.82 (1H, dd, $J = 6.8, 1.2$ Hz, H_{Ar}), 8.10 (1H, dd, $J = 8.4, 1.4$ Hz, H_{Ar}), 8.16 (1H, s, H_{Ar}) ppm. ^{13}C NMR (125 MHz, DMSO- d_6): δ 60.64, 106.74, 114.81, 118.32, 120.73, 122.14, 123.24, 124.64, 126.68, 132.92, 134.48, 137.68, 146.36, 148.62, 152.46, 154.68, 159.03, 162.46 ppm. IR (KBr, cm^{-1}): 3402, 3328, 3188, 2196, 1710, 1676, 1538, 1346. EI-MS: $m/z = 361.07$.

2-Amino-4-(4-nitrophenyl)-5-oxo-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile 4o. M.p. 258–260°C [lit: 255–256°C] [10]. ^1H NMR (500 MHz, DMSO- d_6): δ 4.66 (1H, s, CH), 7.45 (1H, d, $J = 8.3$ Hz, H_{Ar}), 7.50 (1H, t, $J = 7.7$ Hz, H_{Ar}), 7.56 (2H, br s, NH_2), 7.60 (2H, d, $J = 8.0$ Hz, H_{Ar}), 7.76 (1H, t, $J = 7.8$ Hz, H_{Ar}), 7.92 (1H, d, $J = 7.8$ Hz, H_{Ar}), 8.16 (2H, d, $J = 8.3$ Hz, H_{Ar}) ppm. ^{13}C NMR (125 MHz, DMSO- d_6): δ 59.65, 104.64, 114.74, 117.68, 119.78, 123.43, 124.57, 126.56, 131.04, 133.99, 148.46, 152.61, 153.13, 154.81, 158.93, 161.42 ppm. IR (KBr, cm^{-1}): 3482, 3432, 3371, 3340, 2193, 1715, 1673, 1606, 1508, 1372, 1304. EI-MS: $m/z = 361.07$.

2-Amino-4-(4-hydroxyphenyl)-5-oxo-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile 4p. M.p. 259–260°C [lit: 261–262°C] [24]. ^1H NMR (500 MHz, DMSO- d_6): δ 9.53 (1H, s, OH), 4.46 (1H, s, CH), 6.87 (2H, d, $J = 8.1$ Hz, H_{Ar}), 7.18 (2H, d, $J = 8.1$ Hz, H_{Ar}), 7.46 (2H, br s, NH_2), 7.45 (1H, d, $J = 8.3$ Hz, H_{Ar}), 7.49 (1H, t, $J = 7.8$ Hz, H_{Ar}), 7.70 (1H, t, $J = 7.7$ Hz, H_{Ar}), 7.89 (1H, d, $J = 7.7$ Hz, H_{Ar}) ppm. ^{13}C NMR (125 MHz, DMSO- d_6): δ 55.90, 59.10, 105.13, 113.84, 114.71, 117.37, 120.18, 123.29, 125.47, 129.64, 133.66, 136.26, 152.94, 153.94, 158.79, 159.20, 160.38 ppm. IR (KBr, cm^{-1}): 3378, 3314, 3190, 2196, 1710, 1672, 1608. EI-MS: $m/z = 332.03$.

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