An Efficient and Green Synthesis of 6-Amino-3-phenyl-4-aryl-1,4-dihydropyrano [2,3-*c*]pyrazole-5-carbonitrile Derivatives under Ultrasound Irradiation in Aqueous Medium

Yi Zou, Yu Hu, Hai Liu, and Da-Qing Shi*

Key Laboratory of Organic Synthesis of Jiangsu Province, College of Chemistry, Chemical Engineering and Materials Science, Soochow University, Suzhou 215123, People's Republic of China

*E-mail: dqshi@suda.edu.cn

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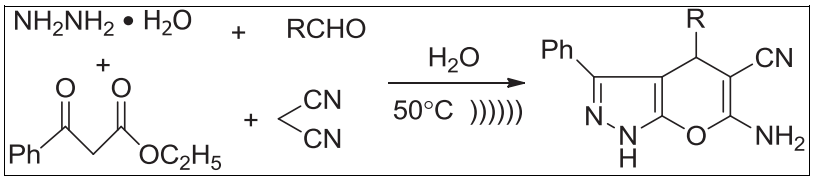

A facile and eco-friendly approach for the synthesis of 6-amino-3-phenyl-4-aryl-1,4-dihydropyrano[2,3-*c*] pyrazole-5-carbonitrile derivatives via four-component reaction of hydrazine, ethyl 3-oxo-3-phenylpropanoate, aldehydes, and malononitrile is described. The reaction is performed in water, without using any catalyst, and under ultrasound irradiation. The developed sonochemical-assisted multi-component reaction provides an improved and accelerated conversion when compared with conventional procedure.

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INTRODUCTION

Industrial chemistry in the new millennium is widely adopting the concept of "Green Chemistry"[1] to meet the fundamental scientific challenges of protecting the human health and environment while maintaining commercial viability. The popularization of ultrasound in life and society is linked to its widespread usage in medicine [2] and chemical synthesis [3] including materials science, aerogels, food chemistry, and other research areas assisted by ultrasound [4]. Recent and innovative applications illustrating the mildness and non-hazardous character of these waves relate to their potential in Green Chemistry. The role of sonochemistry in the creation of "benign-by-design" synthetic methods is clear from the definition: low level of waste, inherently safe, material-saving and energy-saving, with an optimized use of non-renewable resources, and a preferential exploitation of renewable ones. The application of ultrasound in organic synthesis has become increasing because of its advantages such as shorter reaction times, milder reaction condition, and higher yields in comparison with the classical methods [5]. Because in this technique the reaction is carried out normally at lower temperature relative to the usually thermal methods, the possibility of occurrence of undesired reactions is reduced and as a result of a cleaner reaction, the workup is easier. The generation of many cavities and a dramatic increase in the temperature and pressure during collapse of the cavities are the most important effects of ultrasound [6].

Designing organic reactions in aqueous media is another attractive area in green chemistry [7]. Water is an abundant and environmentally benign solvent. As a reaction medium, it offers several benefits including control over exothermic reactions, salting in and salting out, and variation of pH values. Work up and purification can be carried out by simple phase separation techniques. Also, organic reactions in water exhibit unique reactivity and selectivity that are different from reactions in organic solvents.

Dihydropyrano[2,3-*c*]pyrazoles play an essential role in biologically active compounds and therefore represent an interesting template for medicinal chemistry. They have been widely used as medicine intermediates due to their useful biological and pharmacological properties. Many of those compounds are known as antimicrobial [8], insecticidal [9], and anti-inflammatory [10]. Furthermore, dihydropyrano[2,3-*c*]pyrazoles showed molluscicidal activity [11,12] and was identified as a screening hit for Chk1 kinase inhibitor [13]. The first approach to synthesize these substances was undertaken by Otto [14], in which he initiated the reaction sequence by the base-catalyzed cyclization of 4-aryliden-5-pyrazolone. Extending the work of Otto, Klokol, and colleagues [15] performed the direct conversion of 3-methyl-3-pyrazolin-5-one with malononitrile in the presence of a weak base. Sharanin *et al*. [16] developed a three-component reaction between pyrazolone, an aldehyde and malononitrile in ethanol using triethylamine as the catalyst. Shestopalov and co-workers [17] reported the synthesis of pyrazolopyran via a three-component condensation between *N*-methylpiperidone, pyrazoline-5-one, and malononitrile in absolute ethanol. Recently, Laufer and colleagues [18] performed a library of diverse dihydropyrano [2,3-*c*]pyrazoles in ethanol. However, most of these synthetic methods suffer from drawbacks such as employing toxic reagent, strongly basic conditions, expensive and complex catalysts or reagents, many tedious steps, in most

cases, low yields of the products, and long reaction times that restrict their practical applications. As a part of our interest in using water as solvent for organic synthesis and expanding the application of ultrasound in the synthesis of heterocyclic compound [19], herein, we report our preliminary results on exploring a more 'green' and efficient process for the synthesis of 6-amino-3-phenyl-4-aryl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile derivatives.

RESULTS AND DISCUSSION

The choice of an appropriate reaction media is of crucial importance for the successful organic synthesis. To achieve suitable conditions, we investigated the reaction of hydrazine **1**, ethyl 3-oxo-3-phenylpropanoate **2**, 4-methylbenzaldehyde **3a**, and malononitrile **4** as a model reaction substrate in different conditions (Scheme 1). The ultrasonic-assisted reaction to obtain **5a** was examined using different solvents such as ethanol, methanol, acetonitrile, tetrahydrofuran (THF), dioxane, and water, respectively. The results were summarized in Table 1. The reaction could be efficiently carried out in the aforementioned solvents, and the reaction in water gave the best result, affording the desired products not only in good yield but also with higher reaction rates (86% yield in 1 h) (Table 1, entry 6). Hence, all further reactions were carried out using water as solvent, which is considered as the preferential choice of medium for organic reactions in view of economic and environmental problems [20].

We also performed three experiments in steadily increased temperature under ultrasonic irradiation (Table 1) to study the effect of temperature on this reaction. We found that the reaction at 50°C under ultrasound irradiation was the optimal condition for this one-pot reaction and higher temperature did not mean higher yield, because cavitation decreases when increasing the temperature (because of gas evolution) [21].

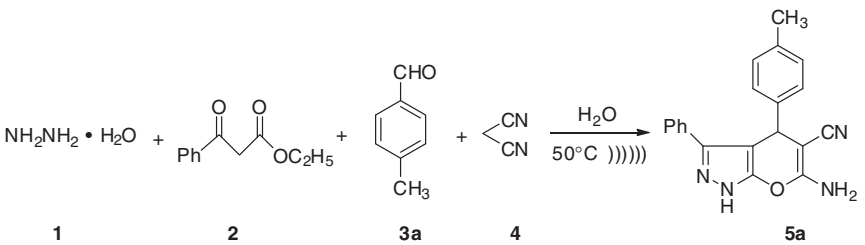
With this optimum condition in hand, we smoothly synthesized 6-amino-3-phenyl-4-aryl-1,4-dihydropyrano[2,3-*c*] pyrazole-5-carbonitrile derivatives in water under sonication (Scheme 2). The results were summarized in Table 2. The reactions proceeded smoothly and a variety of the desired dihydropyrano[2,3-*c*]pyrazoles derivatives products **5** were obtained in good yields whether the aromatic aldehyde **3** is the one bearing electron-withdrawing substituents or electron-donating substituents. In order to verify the effect of ultrasound irradiation, all previously mentioned reactions were carried out under the same conditions in the absence of ultrasound irradiation. The desired products were produced in relatively lowered yields (67–84%) and with much longer reaction time (2–4 h), whereas under ultrasonic irradiation, the products were obtained in 13–37 min with the yields of 70–95%. The method to obtain the desired products under ultrasonic irradiation exhibits several significant advantages including faster reaction rates, higher yields, and higher purity (without any additional purification step) particularly when considering the basic green chemistry concept [22]. Thus, ultrasonic irradiation was found to have beneficial effect on the synthesis of 6-amino-3-phenyl-4-aryl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile derivatives.

In addition, terephthalaldehyde **3l** and isophthalaldehyde **3m** has also been used in this reaction, respectively (Scheme 3), and they all gave the desired products in good yields (Table 3). Unfortunately, the reaction that used phthalaldehyde as aldehyde failed to yield the corresponding products because of large steric hindered effect.

To the best of our knowledge, this new procedure provides the first example of an efficient and ultrasound-promoted approach for the synthesis of 6-amino-3-phenyl-4-aryl-1,4-dihydropyrano [2,3-*c*]pyrazole-5-carbonitrile derivatives in water. This method is the most simple and convenient and would be applicable for the synthesis of different types of nitrogen-containing heterocyclic compounds. The structures of all the synthesized compounds were established by their IR, ^{1}H NMR, ^{13}C NMR, and HRMS spectra.

In this paper, an environmentally benign approach promoted by the synergy of combined use of water and ultrasound offers an easy access to 6-amino-3-phenyl-4-aryl-1,4-dihydropyrano [2,3-*c*]pyrazole-5-carbonitrile derivatives in excellent yields. Ultrasonic irradiation was found to have beneficial effect on the synthesis of these compounds. The reactions proceeded to completion almost instantaneously without the presence of any catalyst, and pure product was obtained, without using any chromatographic techniques, simply by recrystallization from ethanol. We hope that this protocol may be of value to others seeking novel synthetic fragments with unique properties for medicinal chemistry.

Scheme 1. Model reaction.



1 **2** **3a** **4** **5a**

Table 1

The model reaction in different conditions under ultrasound irradiation.[a]

Entry	Solvent	Temperature (°C)	Time (h)	Isolated yield (%)
1	Ethanol	30	1.5	82
2	Methanol	30	2	72
3	Acetonitrile	30	2	31
4	THF	30	2.5	29
5	Dioxane	30	2	35
6	Water	30	1	86
7	Water	50	0.6	90
8	Water	60	0.6	88

[a]Reaction conditions: hydrazine (1.5 mmol), ethyl 3-oxo-3-phenylpropanoate (1 mmol), 4-methylbenzaldehyde (1 mmol), malononitrile (1 mmol), solvent (15 mL) and the ultrasonic power 250 W, irradiation frequency 40 kHz.

EXPERIMENTAL

Commercial solvents and reagents were used as received. Melting points are uncorrected. IR spectra were recorded on Varian F-1000 spectrometer (Varian Inc., Palo Alto, State of California, USA) in KBr with absorptions in cm^{-1}. ^1H NMR was determined on Varian Invoa-400-MHz spectrometer in DMSO-d_6 solution. ^{13}C NMR was determined on Varian Invoa-300/400-MHz spectrometer in DMSO-d_6 solution. *J* values are in Hz. Chemical shifts are expressed in ppm downfield from internal standard tetramethylsilane (TMS). HRMS data were obtained using Bruker microTOF-Q instrument.

Ultrasonication was performed in a KQ-250E medical ultrasound cleaner with a frequency of 40 kHz and an output power of 250 W (Builtin heating, 30–110°C thermostatically adjustable). The reaction flask was located at the maximum energy area in the cleaner, and the surface of the reactants was placed slightly lower than the level of the water. Observation of the surface of the reaction solution during vertical adjustment of vessel depth will show the optimum position by the point at which maximum surface disturbance occurs. The reaction temperature was controlled by addition or removal of water from ultrasonic bath.

Classical procedure for the synthesis of 5 in water. A 100-mL flask was charged with 85% hydrazine hydrate **1** (88 mg, 1.5 mmol), ethyl 3-oxo-3-phenylpropanoate **2** (192 mg, 1 mmol), aldehyde **3** (1 mmol), and malononitrile **4** (66 mg, 1 mmol) in water (15 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 solid.

Ultrasound-promoted synthesis of 5 in water. Another 100-mL flask was charged with 85% hydrazine hydrate **1** (88 mg, 1.5 mmol), ethyl 3-oxo-3-phenylpropanoate **2** (192 mg, 1 mmol), aldehyde **3** (1 mmol), and malononitrile **4** (66 mg, 1 mmol) in water (15 mL). The mixture was sonicated in the water bath of an ultrasonic cleaner 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 solid.

6-Amino-3-phenyl-4-(4-methylphenyl)-1,4-dihydropyrano [2,3-*c*]pyrazole-5-carbonitrile (5a). White powder; mp: 268–270°C; IR (potassium bromide): 3483, 3288, 3114, 2917, 2196, 1639, 1598, 1498, 1400, 1220, 1059, 977, 763 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 2.17 (s, 3H, CH_3), 4.93 (s, 1H, CH), 6.89 (s, 2H, NH_2), 6.99 (s, 4H, ArH), 7.25–7.30 (m, 3H, ArH), 7.45 (d, J = 6.8 Hz, 2H, ArH), 12.88 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 21.22, 37.14, 59.22, 98.19, 121.40, 126.80, 127.84, 128.96, 129.28, 129.62, 136.32, 138.50, 142.43, 156.75, 160.67; HRMS Calcd. for $C_{20}H_{16}N_4ONa$ [M + Na]: 351.1222, found: 351.1232.

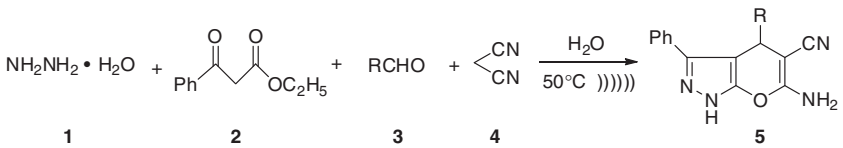
6-Amino-4-(4-methoxyphenyl)-3-phenyl-1,4-dihydropyrano [2,3-*c*]pyrazole-5-carbonitrile (5b). Light yellow powder; mp: 225–227°C (lit.[23] mp: 230°C); IR (potassium bromide): 3411, 3302, 3282, 2192, 1639, 1509, 1449, 1408, 1259, 1170, 1063, 1031 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 3.65 (s, 3H, CH_3O), 4.92 (s, 1H, CH), 6.76 (d, J = 8.4 Hz, 2H, ArH), 6.87 (s, 2H, NH_2), 7.02 (d, J = 8.4 Hz, 2H, ArH), 7.24–7.32 (m, 3H, ArH), 7.45 (d, J = 7.2 Hz, 2H, ArH), 12.87 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 41.54, 60.44, 64.22, 103.22, 119.21, 126.25, 131.71, 133.86, 134.13, 142.34, 143.31, 161.56, 163.33, 165.41; HRMS Calcd. for $C_{20}H_{16}N_4O_2Na$ [M + Na]: 367.1171, found: 367.1166.

6-Amino-4-(4-chlorophenyl)-3-phenyl-1,4-dihydropyrano [2,3-*c*]pyrazole-5-carbonitrile (5c). White powder; mp: 254–256°C (lit.[23] mp: 254°C); IR (potassium bromide): 3435, 3290, 3139, 3065, 2189, 1643, 1597, 1493, 1409, 1218, 1093, 978, 767 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 5.06 (s, 1H, CH), 7.00 (s, 2H, NH_2), 7.12 (d, J = 8.4 Hz, 2H, ArH), 7.24–7.33 (m, 5H, ArH), 7.45 (d, J = 7.2 Hz, 2H, ArH), 12.94 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 41.58, 63.32, 102.48, 126.04, 131.77, 133.84, 133.96, 134.00, 134.16, 134.77, 136.65, 143.57, 149.12, 161.44, 165.65; HRMS Calcd. for $C_{19}H_{13}N_4O^{35}ClNa$ [M + Na]: 371.0676, found: 371.0661.

6-Amino-4-(3-chlorophenyl)-3-phenyl-1,4-dihydropyrano [2,3-*c*]pyrazole-5-carbonitrile (5d). White powder; mp: 241–243°C; IR (potassium bromide): 3461, 3245, 3100, 2923, 2183, 1642, 1594, 1501, 1471, 1408, 1220, 1058, 973, 729 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 5.08 (s, 1H, CH), 7.02 (s, 2H, NH_2), 7.06 (d, J = 7.6 Hz, 1H, ArH), 7.13–7.33 (m, 6H, ArH), 7.46 (d, J = 7.6 Hz, 2H, ArH), 12.94 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 41.64, 62.92, 102.18, 125.87, 131.54, 131.75, 132.60, 133.84, 133.89, 134.01, 135.66, 138.24, 152.44, 161.25, 165.68; HRMS Calcd. for $C_{19}H_{13}N_4O^{35}ClNa$ [M + Na]: 371.0676, found: 371.0680.

6-Amino-4-(2-chlorophenyl)-3-phenyl-1,4-dihydropyrano [2,3-*c*]pyrazole-5-carbonitrile (5e). White powder; mp: 250–251°C; IR (potassium bromide): 3444, 3270, 3122, 2909, 2191, 1638, 1598, 1498, 1397, 1306, 1221, 1058, 977,

Scheme 2. The synthesis of pyrano[2,3-*c*]pyrazole derivatives **5** under sonication.



1 2 3 4 5

Table 2

Synthesis of pyrano[2,3-*c*]pyrazole derivatives **5** under sonication and conventional conditions.

			With US[a]		Without US[b]	
Entry	Product	R	Time (min)	Yield[c] (%)	Time (h)	Yield[c] (%)
1	**5a**	4-$CH_3C_6H_4$	35	90	3	84
2	**5b**	4-$CH_3OC_6H_4$	37	88	3.5	76
3	**5c**	4-ClC_6H_4	15	95	2	80
4	**5d**	3-ClC_6H_4	18	90	2	78
5	**5e**	2-ClC_6H_4	21	85	3	70
6	**5f**	4-FC_6H_4	20	88	3.5	67
7	**5g**	4-BrC_6H_4	13	93	2.5	75
8	**5h**	4-$NO_2C_6H_4$	20	88	4	76
9	**5i**	3,4-$OCH_2OC_6H_3$	30	70	4	69
10	**5j**	3,4-$Cl_2C_6H_3$	18	82	3	70
11	**5k**	2-Thienyl	22	85	3.5	75

[a]Reaction in water at 50°C under ultrasound irradiation.
[b]Reaction in water at 50°C under high-stirring condition.
[c]Yields of isolated products.

686 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 5.43 (s, 1H, CH), 7.00 (s, 2H, NH_2), 7.10–7.18 (m, 3H, ArH), 7.25–7.31 (m, 4H, ArH), 7.37 (d, J = 6.8 Hz, 2H, ArH), 12.91 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 39.46, 61.93, 102.03, 125.54, 131.50, 132.96, 133.58, 133.92, 134.80, 136.07, 137.45, 143.35, 146.53, 161.62, 165.92; HRMS Calcd. for $C_{19}H_{13}N_4O^{35}ClNa$ [M + Na]: 371.0676, found: 371.0670.

6-Amino-4-(4-fluorophenyl)-3-phenyl-1,4-dihydropyrano [2,3-*c*]pyrazole-5-carbonitrile (5f). White powder; mp: 246–248°C; IR (potassium bromide): 3496, 3240, 3095, 2192, 1638, 1601, 1587, 1502, 1406, 1222, 1062, 975, 827 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 5.04 (s, 1H, CH), 6.96 (s, 2H, NH_2), 7.01 (t, J = 8.8 Hz, 2H, ArH), 7.12–7.15 (m, 2H, ArH), 7.24–7.32 (m, 3H, ArH), 7.44 (d, J = 7.2 Hz, 2H, ArH), 12.91 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 36.61, 58.78, 97.95, 115.56, 115.56, 115.84, 121.23, 126.93, 129.03, 129.19, 129.24, 129.83, 129.94, 138.68, 141.45, 141.49, 156.56, 159.84, 160.71, 163.06; HRMS Calcd for $C_{19}H_{13}N_4OFNa$ [M + Na]: 355.0966, found: 355.0970.

6-Amino-4-(4-bromophenyl)-3-phenyl-1,4-dihydropyrano [2,3-*c*]pyrazole-5-carbonitrile (5g). White powder; mp: 230–232°C; IR (potassium bromide): 3431, 3286, 3135, 2874, 2187, 1643, 1599, 1499, 1483, 1414, 1219, 1065, 1013, 976 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 5.05 (s, 1H, CH), 6.99 (s, 2H, NH_2), 7.07 (d, J = 8.0 Hz, 2H, ArH), 7.25–7.33 (m, 3H, ArH), 7.38 (d, J = 8.4 Hz, 2H, ArH), 7.46 (d, J = 7.2 Hz, 2H, ArH), 12.93 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 36.78, 58.39, 97.54, 120.34, 121.16,

Scheme 3. Synthesis of bispyrano[2,3-*c*]pyrazole derivatives.

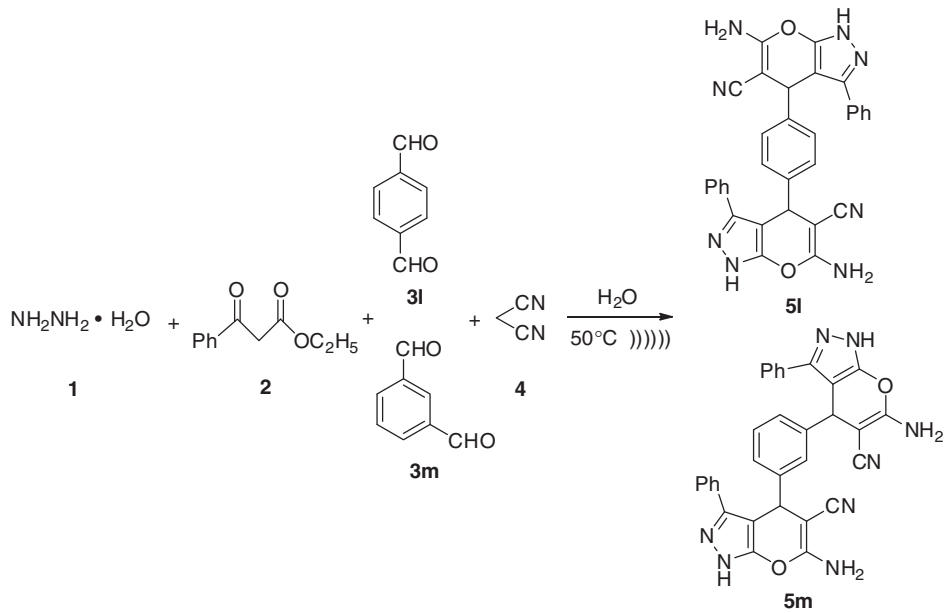


Table 3

Synthesis of bispyrano[2,3-*c*]pyrazole derivatives under sonication and conventional conditions.

			With US		Without US	
Entry	Product	Aldehyde	Time (min)	Yield[a] (%)	Time (h)	Yield[a] (%)
1	**5l**	Terephthalaldehyde	23	92	3	75
2	**5m**	Isophthalaldehyde	30	85	5	70

[a]Yields of isolated products.

126.88, 129.13, 129.30, 130.26, 131.88, 138.68, 144.67, 156.57, 160.78; HRMS Calcd. for $C_{19}H_{13}N_4O^{79}BrNa$ [M + Na]: 415.0165, found: 415.0159.

6-Amino-4-(4-nitrophenyl)-3-phenyl-1,4-dihydropyrano [2,3-*c*]pyrazole-5-carbonitrile (5h). White powder; mp: 224–226°C; IR (potassium bromide): 3438, 3286, 3122, 2871, 2186, 1646, 1597, 1515, 1419, 1351, 1066, 977, 768 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 5.27 (s, 1H, CH), 7.12 (s, 2H, NH_2), 7.24–7.32 (m, 3H, ArH), 7.39 (d, J = 8.4 Hz, 2H, ArH), 7.46 (d, J = 7.2 Hz, 2H, ArH), 13.01 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 36.95, 57.54, 96.95, 120.96, 124.35, 126.90, 128.96, 129.22, 129.36, 138.91, 146.87, 152.74, 156.50, 161.04; HRMS Calcd for $C_{19}H_{13}N_5O_3Na$ [M + Na]: 382.0911, found: 382.0930.

6-Amino-4-(benzo[*d*][1,3]dioxol-5-yl)-3-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (5i). White powder; mp: 231–232°C; IR (potassium bromide): 3481, 3435, 3205, 3132, 2897, 2189, 1633, 1601, 1501, 1446, 1401, 1252, 1041, 926, 728 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 4.93 (s, 1H, CH), 5.91 (d, J = 4.4 Hz, 2H, OCH_2O), 6.57–6.61 (m, 2H, ArH), 6.72 (d, J = 8.0 Hz, 1H, ArH), 6.90 (s, 2H, NH_2), 7.27–7.34 (m, 3H, ArH), 7.47 (d, J = 7.6 Hz, 2H, ArH), 12.89 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 37.04, 59.10, 98.08, 101.52, 108.19, 108.58, 121.16, 126.90, 129.02, 129.28, 138.52, 139.46, 146.46, 147.83, 156.63, 160.64; HRMS Calcd. for $C_{20}H_{14}N_4O_3Na$ [M + Na]: 381.0958, found: 381.0959.

6-Amino-4-(3,4-dichlorophenyl)-3-phenyl-1,4-dihydropyrano [2,3-*c*]pyrazole-5-carbonitrile (5j). White powder; mp: 248–249°C; IR (potassium bromide): 3477, 3250, 3111, 2903, 2190, 1633, 1590, 1500, 1468, 1403, 1218, 1179, 1058, 973, 893, 738 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 5.14 (s, 1H, CH), 7.08 (s, 3H, ArH), 7.27–7.48 (m, 7H, ArH and NH_2), 12.97 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 36.45, 57.81, 97.05, 121.12, 127.01, 129.25, 129.95, 130.03, 131.52, 138.97, 146.12, 156.43, 161.02; HRMS Calcd. for $C_{19}H_{12}N_4O^{35}Cl_2Na$ [M + Na]: 405.0280, found: 405.0270.

6-Amino-3-phenyl-4-(thiophen-2-yl)-1,4-dihydropyrano [2,3-*c*]pyrazole-5-carbonitrile (5k). White powder; mp: 232–234°C; IR (potassium bromide): 3467, 3200, 3130, 2205, 1631, 1599, 1500, 1483, 1399, 1222, 1058, 975, 756 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 5.41 (s, 1H, CH), 6.81 (s, 1H, ArH), 6.90 (s, 1H, ArH), 7.05 (s, 2H, NH_2), 7.23 (d, J = 4.4 Hz, 1H, ArH), 7.30–7.35 (s, 3H, ArH), 7.54 (d, J = 7.2 Hz, 2H, ArH), 12.97 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 32.74, 58.98, 98.23, 121.24, 125.01, 125.46, 126.99, 127.14, 129.17, 129.36, 138.96, 150.28, 156.02, 160.81; HRMS Calcd. for $C_{17}H_{13}N_4OS$ [M + H]: 321.0805, found: 321.0803.

4,4′-(1,4-Phenylene)bis(6-amino-3-phenyl-1,4-dihydropyrano [2,3-*c*]pyrazole-5-carbonitrile) (5l). Yellow powder; mp: >300°C; IR (potassium bromide): 3293, 3049, 2946, 2188, 1654, 1638, 1589, 1508, 1476, 1277, 1065, 975 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 4.80 (s, 1H, CH), 4.83 (s, 1H, CH), 6.90 (s, 2H, NH_2), 6.92 (s, 2H, NH_2), 6.99–7.01 (m, 4H, ArH), 7.12–7.25 (m, 10H, ArH), 12.86 (s, 1H, NH), 12.89 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 37.11, 58.89, 58.94, 97.98, 97.98, 121.23, 121.29, 126.72, 126.88, 128.06, 128.14, 128.89, 129.20, 138.45, 138.71, 143.88, 144.06, 156.66, 160.58, 160.70; HRMS Calcd. for $C_{32}H_{22}N_8O_2Na$ [M + Na]: 573.1758, found: 573.1768.

4,4′-(1,3-Phenylene)bis(6-amino-3-phenyl-1,4-dihydropyrano [2,3-c]pyrazole-5-carbonitrile) (5m). White powder; mp: >300°C; IR (potassium bromide): 3477, 3370, 3247, 2194, 1639, 1598, 1499, 1479, 1399, 1216, 1057, 977, 768 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 4.76 (s, 1H, CH), 4.84 (s, 1H, CH), 6.76–6.82 (m, 1H, ArH), 6.89–6.93 (m, 5H, ArH and 2 × NH_2), 7.07 (m, 1H, ArH), 7.18–7.31 (m, 11H, ArH), 12.80 (s, 1H, NH), 12.92 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 37.41, 37.67, 58.85, 58.98, 97.87, 97.92, 121.00, 121.14, 126.34, 126.43, 126.80, 126.99, 127.26, 128.73, 128.91, 129.12, 129.22, 129.35, 138.27, 138.83, 145.49, 145.74, 156.60, 156.93, 160.67; HRMS Calcd. for $C_{32}H_{22}N_8O_2Na$ [M + Na]: 573.1758, found: 573.1768.

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