One-pot, Three-component Synthesis of a New Series of 2-Amino-4-aroyl-5-oxo-5,6-dihydro-2*H*-pyrano[3,2-*c*]quinoline-3-carbonitrile in the Presence of SBA-15 as a Nanocatalyst

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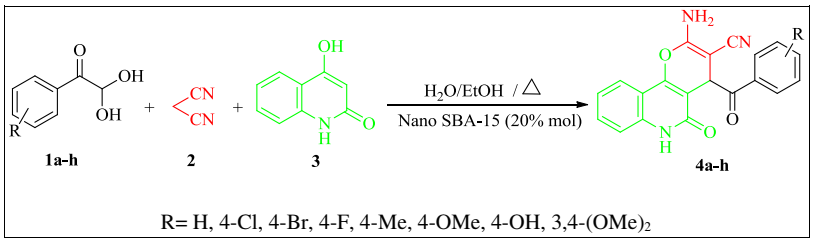

One-pot, three-component reaction of arylglyoxals, malononitrile and 4-hydroxyquinolin-2(1*H*)-one in the presence of SBA-15 as a nanocatalyst and using green solvent systems under various temperatures afforded the 2-amino-4-aroyl-5-oxo-5,6-dihydro-2*H*-pyrano[3,2-c]quinoline-3-carbonitrile derivatives. The best yield (70-96%) were obtained using 20% mol of SBA-15 as a nanocatalyst in H2O/EtOH (1:1) at 80 °C. The simplicity of work up procedure, using green solvent system, and good to excellent yields of products are the main advantages of this synthetic strategy.

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INTRODUCTION

Pyranoquinoline moiety is present in many alkaloids that have attracted great attention because of their interesting biological and pharmacological properties, such as antitumor [1,2], antimicrobial [3], anti-inflammatory [4], antiallergic [5], antimalarial [6] inhibition of calcium signaling [7], and platelet aggregation [8].

Furthermore, many of these alkaloids exhibit cancer cell growth inhibitory activity and are investigated as potential anticancer agents [9]. Pyranoquinoline derivatives are also useful intermediates in the manufacture of azo dyestuffs and can be used for dyeing of both naturally occurring and synthetic fibers [10].

Recently, multicomponent reactions have attracted much attention because of their highly creative manner in synthesis of complex molecules, with multiple bond making/bond breaking just in one single step, without the complicated purification and with economically favorable processes [11,12]. However, multicomponent reactions in green solvents and using green catalysts will be a powerful tool in organic synthesis.

In continuation of our interests in synthesis of new heterocyclic compounds by one-pot, multicomponent reactions [13–17], herein, we report the one-pot, three-component synthesis of a new series of 2-amino-4-aroyl-5-oxo-5,6-dihydro-2*H*-pyrano[3,2-*c*]quinoline-3-carbonitrile in the presence of SBA-15 as a nanocatalyst.

RESULTS AND DISCUSSION

In our initial studies, the reaction of 4-methyl phenylglyoxal monohydrate (**1e**), malononitrile (**2**), and 4-hydroxyquinolin-2(1*H*)-one (**3**) was chosen as a trail reaction (Scheme 1), and by stirring the reaction mixture at room temperature, we did not observe any desired product formation even after 24 h. The reaction was carried out using various amounts of catalysts and different solvent systems as mentioned in Table 1. A solid precipitate (**4e**) was separated out in 15–96% yield, which was characterized by its spectral data to be the desired 2*H*-pyrano[3,2-*c*]quinoline.

The best result was obtained in terms of yield (96%) and reaction time (4 h), when the reaction was carried out using 20% mol of SBA-15 as a nanocatalyst in H_2O/EtOH (1:1) (Table 1, entry 3). To study the effect of the amount of catalyst, the reaction was carried out with different amounts of SBA-15 ranging from 15 to 30% mol, and the best condition was using 20% mol of catalyst in H_2O/EtOH (1:1). Increasing the amount of catalyst did not improve the yield.

To find the best solvent system for this reaction, we carried out the trail reaction using various solvents such as, EtOH, H_2O, H_2O/EtOH (1:1), and H_2O/EtOH (1:2) as shown in Table 1.

Among all these solvents, H_2O/EtOH (1:1) was proved to be the best solvent system for this reaction in terms of yield (Table 1, entry 3).

Scheme 1. The trial reaction for synthesis of **4**. [Color figure can be viewed at wileyonlinelibrary.com]

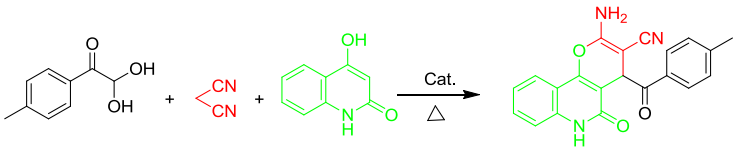


Table 1

Optimization of the reaction conditions.

Entry	Solvents	Temperature (°C)	Catalyst (% mol)	Time (h)	Yields (%)
1	H_2O/EtOH (1:1)	80	SBA-15 (10)	7	91
2	H_2O/EtOH (1:1)	80	SBA-15 (15)	6	92
3	**H_2O/EtOH (1:1)**	**80**	**SBA-15 (20)**	**4**	**96**
4	H_2O/EtOH (1:1)	80	SBA-15 (25)	4	95
5	H_2O/EtOH (1:2)	80	SBA-15 (20)	6	91
6	H_2O	Reflux	SBA-15 (20)	6	44
7	EtOH	Reflux	SBA-15 (20)	6	15
8	H_2O/EtOH	80	L-proline	10	80

Bold values shows the best reaction conditions in terms of yield, solvent system and reaction time in trial reaction.

Using an amino acid L-proline as an organocatalyst provided lower yield (Table 1, entry 8).

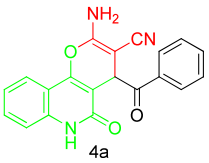
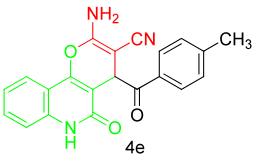
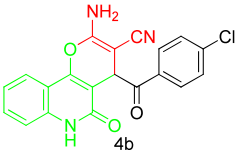
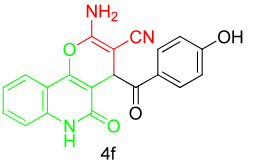
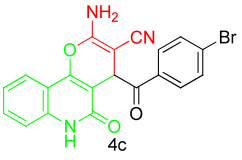
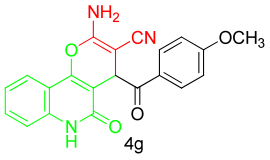
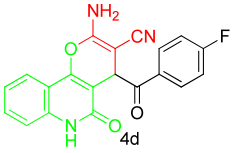
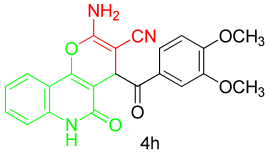
After optimizing the reaction condition, we next verified the scope of this reaction with various arylglyoxals to form our desired pyranoquinoline derivatives **4a–h**.

The reaction conditions and the yields of products are listed in Table 2.

The structures of substituted 2-amino-4-aroyl-5-oxo-5, 6-dihydro-2*H*-pyrano[3,2-*c*]quinoline-3-carbonitriles **4a–h** were characterized by their Fourier transform infrared

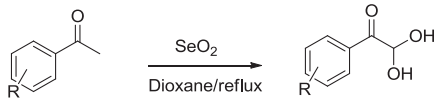
Table 2

Substituted 2*H*-pyrano[3,2-*c*]quinolines.

Entry	Pyrano[3,2-*c*]quinolines	Reaction time (h)	Entry	Pyrano[3,2-*c*]quinolines	Reaction time (h)
1	 4a	6	5	 4e	4
2	 4b	6	6	 4f	5
3	 4c	5	7	 4g	4
4	 4d	5	8	 4h	5

(FTIR), ^{1}H-NMR, and ^{13}C-NMR spectral data. The characteristic singlet at δ 11.83–11.90 and δ 5.25–5.36 ppm was ascribed to the NH group and CH of the pyranoquinoline moiety, respectively, and was present in all new products. In the ^{13}C-NMR spectra of the products **4a–h**, signals located at δ 196–199 ppm were attributed to the carbonyl groups of arylglyoxal moieties. In the FTIR spectra, the characteristic absorption bonds at 3337–3468, 3010–3189, and 2188–2203 cm^{-1} could be assigned to the vibrations of NH, NH_2, and CN groups, respectively (Scheme 1).

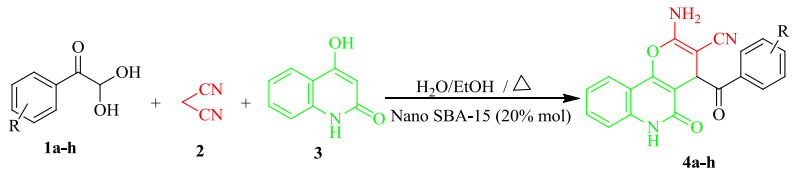
Scheme 2. Preparation of arylglyoxal monohydrates.



The various arylglyoxal monohydrates **1a–h** were prepared from the corresponding acetophenones by oxidation procedure with selenium dioxide via the literature procedure as shown in Scheme 2 [18].

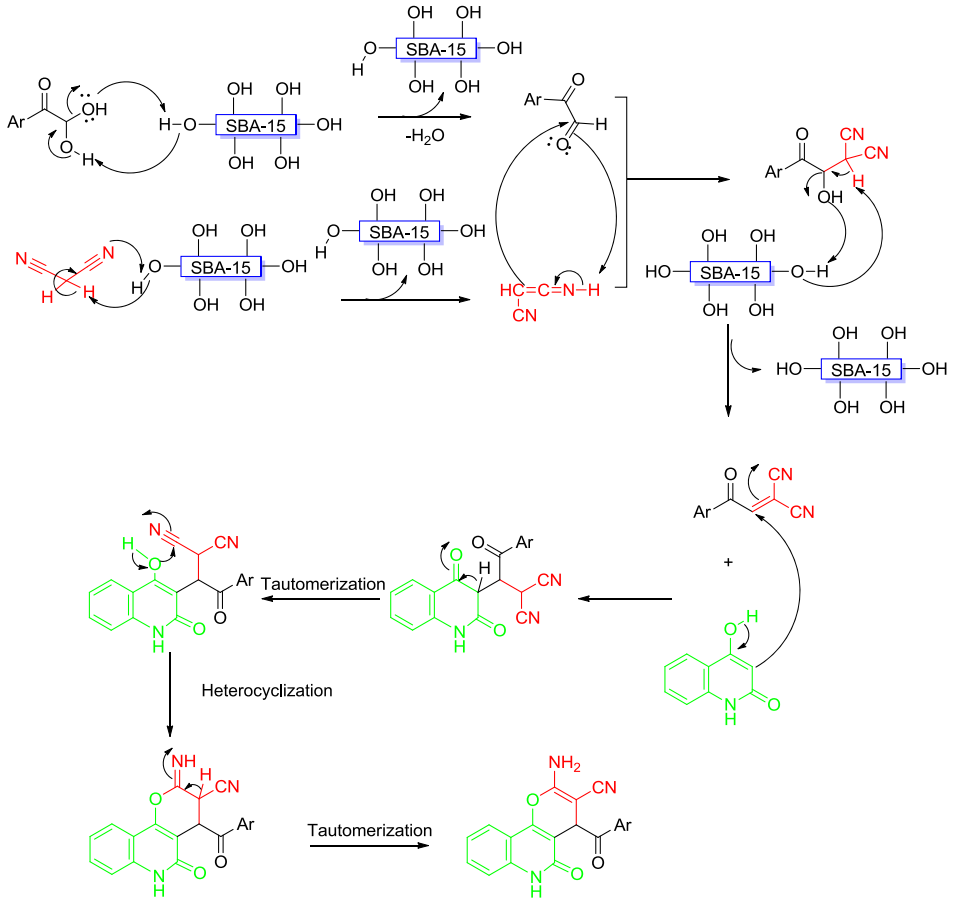
The one-pot,three-component reaction of arylglyoxal hydrates **1a–h**, malononitrile (**2**), and 4-hydroxyquinolin-2(1*H*)-one (**3**) in H_2O/EtOH (1:1) in the presence of

Scheme 3. One-pot synthesis of substituted 2*H*-pyrano[3,2-*c*]quinoline derivatives. [Color figure can be viewed at wileyonlinelibrary.com]



R= H, 4-Cl, 4-Br, 4-F, 4-Me, 4-OMe, 4-OH, 3,4-$(OMe)_2$

Scheme 4. The proposed mechanism for synthesis of substituted 2*H*-pyrano[3,2-*c*]quinolines catalyzed by SBA-15 as a nanocatalyst. [Color figure can be viewed at wileyonlinelibrary.com]



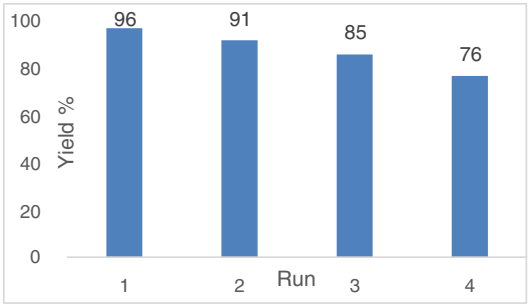


Figure 1. Reusability of SBA-15 for the synthesis of pyrano[3,2-*c*]quinoline derivatives. [Color figure can be viewed at wileyonlinelibrary.com]

nanocatalyst SBA-15 (20% mol) gave the corresponding 2*H*-pyrano[3,2-*c*]quinolines in 70–98% yield as shown in Scheme 3.

The proposed mechanism of the reaction involves the initial condensation of arylglyoxals with malononitrile, followed by reaction of the intermediate with 4-hydroxyquinolin-2(1*H*)-one, leading to the formation of the desired products through intermolecular cyclization and subsequent tautomerization as shown in Scheme 4.

The reusability of nanocatalyst is shown in Figure 1.

CONCLUSION

We have reported, one-pot,three-component synthesis of a new series of 2-amino-4-aroyl-5-oxo-5,6-dihydro-2*H*-pyrano[3,2-*c*]quinoline-3-carbonitrile derivatives in the presence of SBA-15 as a nanocatalyst.

The simplicity of the workup process and isolation of catalysts along with using green solvents and good to high yields are the advantages of this protocol.

EXPERIMENTAL

Melting points were measured on a Philip Harris C4954718 apparatus and are uncorrected. Infrared spectra were recorded on a Thermo-Nicolet Nexus 670 FTIR instrument using KBr discs. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker Avance AQS 300-MHz spectrometer at 300 and 75.5 MHz, respectively. Chemical shifts were measured in DMSO-d_6 using tetramethylslane as the internal standard. The reaction monitoring was accomplished via thin-layer chromatography on silica gel PolyGram SILG/UV254 plates. Elemental analyses were performed using a Leco Analyzer 9320.

General procedure for synthesis of new pyranoquinoline derivatives. The arylglyoxal hydrates (1 mmol) was dissolved in H_2O/EtOH (1:1) (6 mL), and then malononitrile (1 mmol), 4-hydroxyquinolin-2(1*H*)-one (1 mmol), and nanocatalyst (SBA-15) (20% mol) were added to the reaction mixture.

The reaction mixture was heated up to 80°C for appropriate time as indicated in Table 2. The reaction completion was monitored by thin-layer chromatography using (EtOAc/hexane 2:3) as eluent. The precipitate was filtered and washed with water then recrystallized from EtOH to give the desired products as white to pale yellow needles in 70–98% yields.

Separation of catalyst. The solvent of filtrate was evaporated, and the residue was washed with cold ethanol (2 × 2 mL) and dried to give the catalyst as white solid, which was used for checking its reusability (Fig. 1).

2-Amino-4-benzoyl-5-oxo-5,6-dihydro-4H-pyrano[3,2-c] quinoline-3-carbonitrile (4a). Yield: 70%; white powder; mp 290–292°C. υ_{max} (KBr): 3352, 3189, 2199, 1672, 1629, 1593, 1496, 1441, 1384, 1327, 1258, 1173, 1118, 1023 cm^{-1}; δ_H (300 MHz, DMSO-d_6), 11.90 (s, 1H, NH), 8.11 (d, *J* = 9.2 Hz, 2H, Ar), 7.86 (d, *J* = 9.0 Hz, 1H, Ar), 7.96 (t, *J* = 6.0 Hz, 1H, Ar), 7.55–7.64 (m, 4H, NH_2 + 2Ar-H), 7.47 (bs, 1H, Ar), 7.28–7.38 (m, 2H, Ar), 5.35 (s, 1H, CH); δ_C (75 MHz, DMSO-d_6), 199.1, 161.1, 161.0, 160.6, 152.6, 138.2, 138.1, 136.2, 134.1, 131.9, 129.4, 129.2, 122.7, 121.9, 119.5, 115.9, 112.2, 107.8, 52.1, 37.5. Found: %C, 70.13, %H, 3.69, %N, 12.41. $C_{20}H_{13}N_3O_3$ requires %C, 69.96, %H, 3.82, %N, 12.24.

2-Amino-4-(4-chlorobenzoyl)-5-oxo-5,6-dihydro-4H-pyrano [3,2-c]quinoline-3-carbonitrile (4b). Yield: 75%; yellow powder; mp 270–272°C. υ_{max} (KBr): 3466, 3339, 3190, 2845, 2202, 1671, 1583, 1496, 1382, 1324, 1261, 1176, 1109, 1023 cm^{-1}; δ_H (300 MHz, DMSO-d_6),11.89 (s, 1H, NH), 8.14 (d, *J* = 7.5 Hz, 2H, Ar), 7.87 (d, *J* = 7.8 Hz, 1H, Ar), 7.65 (d, *J* = 7.5 Hz, 2H, Ar), 7.60 (t, *J* = 7.2 Hz, 1H, Ar), 7.48 (bs, 2H, NH_3), 7.31 (t, *J* = 7.2 Hz, 2H, Ar), 5.35 (s, 1H, CH); δ_C (75 MHz, DMSO-d_6), 198.4, 161.1, 160.6, 152.6, 139.2, 138.2, 135.0, 131.9, 131.3, 129.5, 129.3, 122.7, 121.9, 119.5, 116.0, 112.2, 107.6, 51.9, 37.6. Found: %C, 63.71, %H, 3.04, %N, 11.28. $C_{20}H_{12}ClN_3O_3$ requires %C, 63.59, %H, 3.20, %N, 11.12.

2-Amino-4-(4-bromobenzoyl)-5-oxo-5,6-dihydro-4H-pyrano [3,2-c]quinoline-3-carbonitrile (4c). Yield 90%; white powder; mp 285–287°C. υ_{max} (KBr): 3472, 3361, 2843, 2177, 1660, 1592, 1505, 1390, 1322, 1230, 1155, 1113, 1020 cm^{-1}; δ_H (300 MHz, DMSO-d_6), 11.89 (s, 1H, NH), 8.05 (d, *J* = 9.0 Hz, 2H, Ar), 7.86 (d, *J* = 6.0 Hz, 1H, Ar), 7.80 (d, *J* = 6.0 Hz, 2H, Ar), 7.59 (d, *J* = 9.0 Hz, 1H, Ar), 7.48 (bs, 2H, NH_2), 7.35 (m, 2H, Ar), 5.34 (s, 1H, CH); δ_C (75 MHz, DMSO-d_6), 198.6, 161.14, 160.6, 152.6, 138.2, 135.4, 132.3, 131.9, 131.4, 130.6, 128.4, 119.5, 116.0, 112.2, 107.6, 51.9, 37.9. Found: %C, 56.98, %H, 2.69, %N, 10.11. $C_{20}H_{12}BrN_3O_3$ requires %C, 56.89, %H, 2.86, %N, 9.95.

2-Amino-4-(4-fluorobenzoyl)-5-oxo-5,6-dihydro-4H-pyrano [3,2-c]quinoline-3-carbonitrile (4d). Yield 88%; yellow powder; mp 260–263°C. υ_{max} (KBr): 3468, 3321, 2863,

2188, 1673, 1593, 1501, 1390, 1320, 1230, 1160, 1113, 1023 cm^{-1}; δ_H (300 MHz, DMSO-d_6), 11.89 (s, 1H, NH), 8.23 (t, *J* = 7.2 Hz, 2H, Ar), 7.87 (d, *J* = 8.1 Hz, 1H, Ar), 7.61 (t, *J* = 7.8 Hz, 1H, Ar), 7.46 (bs, 2H, NH_2), 7.40 (d, *J* = 8.4 Hz, 1H, Ar), 7.36 (t, *J* = 8.1 Hz, 2H, Ar), 7.32 (t, *J* = 7.5 Hz, 1H, Ar), 5.36 (s, 1H, CH); δ_C (75 MHz, DMSO-d_6), 197.8, 167.5, 164.1, 161.1, 160.6, 152.6, 138.2, 133.1, 132.5, 132.4, 131.9, 122.7, 121.9, 119.5, 116.4, 116.1, 116.0, 112.2, 107.7, 52.1, 37.6. Found: %C, 66.63, %H, 3.22, %N, 11.78. $C_{20}H_{12}FN_3O_3$ requires %C, 66.48, %H, 3.35, %N, 11.63.

2-Amino-4-(4-methylbenzoyl)-5-oxo-5,6-dihydro-4H-pyrano[3,2-c]quinoline-3-carbonitrile (4e). Yield 96%; yellow powder; mp 260–262°C. υ_{max} (KBr): 3453, 3300, 3172, 2191, 1668, 1499, 1388, 1315, 1251, 1178, 1113, 1034 cm^{-1}; δ_H (300 MHz, DMSO-d_6), 1.86 (s, 1H, NH), 8.01 (d, *J* = 7.8 Hz, 2H, Ar), 7.86 (d, *J* = 9.0 Hz, 1H, Ar), 7.60 (t, *J* = 6.0 Hz, 1H, Ar), 7.42 (bs, 2H, NH_2), 7.29–7.39 (m, 4H, Ar), 5.31 (s, 1H, CH), 2.41 (s, 3H, CH_3); δ_C (75 MHz, DMSO-d_6), 198.5, 161.1, 160.6, 152.6, 144.6, 138.2, 133.7, 131.8, 129.7, 129.6, 122.6, 121.9, 119.6, 116.0, 112.3, 107.9, 52.4, 37.5, 21.6. Found: %C, 70.73, %H, 4.18, %N, 11.89. $C_{21}H_{15}N_3O_3$ requires %C, 70.58, %H, 4.23, %N, 11.76.

2-Amino-4-(4-hydroxybenzoyl)-5-oxo-5,6-dihydro-4H-pyrano[3,2-c]quinoline-3-carbonitrile (4f). Yield 90%; yellow powder; mp 295–300°C. υ_{max} (KBr): 3418, 3221, 2194, 1678, 1575, 1387, 1322, 1234, 1164, 1116 cm^{-1}; δ_H (300 MHz, DMSO-d_6), 11.83 (s, 1H, NH), 10.47 (s, 1H, OH), 8.00 (d, *J* = 8.4 Hz, 2H, Ar), 7.86 (d, *J* = 9.0 Hz, 1H, Ar), 7.59 (t, *J* = 9.0 Hz, 1H, Ar), 7.37 (bs, 2H, NH_2), 7.28–7.34 (m, 2H, Ar), 6.89 (d, *J* = 9.0 Hz, 2H, Ar), 5.25 (s, 1H, CH); δ_C (75 MHz, DMSO-d_6), 196.8, 163.0, 161.1, 160.6, 152.7, 138.2, 132.2, 131.7, 127.6, 122.6, 121.8, 119.6, 115.9, 115.7, 112.3, 108.1, 52.7, 37.0. Found: %C, 66.98, %H, 3.49, %N, 11.84. $C_{20}H_{13}N_3O_4$ requires %C, 66.85, %H, 3.65, %N, 11.69.

2-Amino-4-(4-methoxybenzoyl)-5-oxo-5,6-dihydro-4H-pyrano[3,2-c]quinoline-3-carbonitrile (4g). Yield 98%; white powder; mp 280–284°C. υ_{max} (KBr): 3337, 3185, 2837, 2203, 1674, 1629, 1596, 1382, 1325, 1261, 1171, 1117, 1028 cm^{-1}; δ_H (300 MHz, DMSO-d_6), 11.84 (s, 1H, NH), 8.10 (bd, 2H, *J* = 6.9 Hz, Ar), 7.86 (d, *J* = 6.3 Hz, 1H, Ar), 7.59 (d, *J* = 7.0 Hz, 1H, Ar), 7.20–7.50 (m, 4H, NH_2 + 2Ar-H), 7.09 (d, *J* = 6.9 Hz, 2H, Ar), 5.29 (s, 1H, CH), 3.86 (s, 3H, CH_3); δ_C (75 MHz, DMSO-d_6), 197.2, 164.0, 161.1, 160.6, 152.6, 138.2, 131.9, 129.0, 122.6, 121.9, 119.6, 116.0, 114.4, 112.3, 108.0, 56.0, 52.5, 37.2. Found: %C, 67.73, %H, 3.92, %N, 11.40. $C_{21}H_{15}N_3O_4$ requires %C, 67.56, %H, 4.05, %N, 11.25.

2-Amino-4-(3,4-dimethoxybenzoyl)-5-oxo-5,6-dihydro-4H-pyrano[3,2-c]quinoline-3-carbonitrile (4h). Yield 85%; yellow powder; mp 280–285°C. υ_{max} (KBr): 3407, 3288, 3173, 2832, 2196, 1672, 1629, 1587, 1510, 1384, 1260, 1161, 1118, 1022 cm^{-1}; δ_H (300 MHz, DMSO-d_6), 11.86 (s, 1H, NH), 7.85 (t, *J* = 9.0 Hz, 2H, Ar), 7.58 (d, *J* = 9.0 Hz, 2H, Ar), 7.41 (bs, 2H, NH_2), 7.28–7.38 (m, 2H, Ar), 7.13 (d, *J* = 9.0 Hz, 1H, Ar), 5.31 (s, 1H, CH), 3.88 (s, 3H, CH_3), 3.83 (s, 3H, CH_3); δ_C (75 MHz, DMSO-d_6), 197.0, 162.3, 161.1, 160.7, 154.0, 152.7, 148.9, 138.2, 131.8, 128.8, 122.6, 119.7, 116.0, 112.3, 111.6, 111.3, 108.1, 56.2, 55.9, 52.6, 37.2. Found: %C, 65.63, %H, 4.08, %N, 10.56. $C_{22}H_{17}N_3O_5$ requires %C, 65.50, %H, 4.25, %N, 10.42.

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