# A new three-component coupling reaction of aryl glyoxal, malononitrile, and 4-hydroxy coumarin catalysed by recyclable $TiO_2$ nanoparticles

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Aryl glyoxals reacted with malononitrile and 4-hydroxycoumarin in the presence of a catalytic amount of $TiO_2$ nanoparticles to give a hitherto unknown family of pyranochromenes in up to 80% yield. This new three-component reaction yielded some novel pyrano[3,2-c]chromene-5-ones containing an aroyl substituent. Using a recyclable and safe catalyst along with a green solvent system made the process eco-friendly and economic.

**Keywords:** aryl glyoxal, pyrano[3,2-c]chromene-5-one, $TiO_2$ nanoparticle catalyst

Multicomponent reactions (MCRs) have attracted the attention of many organic chemists because they allow the creation of several bonds in a single operation and offer considerable advantages such as operational simplicity, convergence, facile automation, reduction in the number of workup, extraction and purification processes, and hence minimise waste generation, rendering the transformations green.[1–3] Coumarins fused with other heterocycles are important compounds due to their special biological and photodynamic properties.[4–7] Among coumarin fused heterocycles, pyrano[3,2-*c*]chromene-5-ones represent a promising class of synthetic targets because of their interesting biological properties.[8,9] To date, many synthetic methodologies for the synthesis of this class of compounds have been studied by many research groups. Generally, pyrano[3,2-*c*]chromene-5-ones are accessible *via* a three-component reaction of 4-hydroxycoumarin, aromatic aldehydes and active methylenes compounds.[10–14] In recent years, nanocatalysts have attracted special attention due to their greater efficiency in comparison with their bulk case counterparts. Among nanocatalysts, $TiO_2$ nanoparticles as safe metal oxide materials were used for several organic reactions and showed high efficiency.[15–17] To our knowledge, there is no report on the synthesis of pyrano[3,2-*c*]chromene-5-ones starting from aryl glyoxals instead of aromatic aldehydes. Here, by deployment of $TiO_2$ NPs, a green three-component strategy to produce a novel class of pyrano[3,2-*c*]chromene-5-ones containing an aryloyl group is described.

## Results and discussion

Among nano-sized transition metal oxides, titanium oxide nanoparticles ($TiO_2$ NPs) have gained importance as they exhibit interesting catalytic properties which cannot be achieved by their bulk counterparts. $TiO_2$ is not classified as hazardous according to the United Nations' (UN) Globally Harmonized System of Classification and Labeling of Chemicals and is a water-insoluble material which can be recovered and reused, thereby reducing waste. Figure 1 (A) shows the X-ray diffraction pattern for titanium dioxide nanoparticles. Six diffraction peaks at 25.18º, 37.71º, 47.81º, 54.81º, 61.39º, and 69.99º and intensity of the characteristic peaks of the samples are in good agreement with the standard data for the $TiO_2$ nanoparticle structure. The scanning electron microscope (SEM) image of $TiO_2$ nanoparticles is shown in Fig. 1 (B). The nanoparticles have spherical shape with average diameter of 50 nm.

As a part of our programs for developing green organic methodologies,[18] especially the synthesis of heterocyclic compounds,[19] we have investigated the synthesis of pyrano[3,2-*c*]chromene-5-ones **4** as a novel class of pyrano fused heterocycles containing an aryloyl substituent *via* a one-pot, three-component reaction of 4-hydroxycoumarin (**1**), an aryl glyoxal **2** and malononitrile (**3**) in the presence of $TiO_2$ NPs (Scheme 1). We found that the reactions proceeded with selectivity and the expected product **4** was formed in high yield.

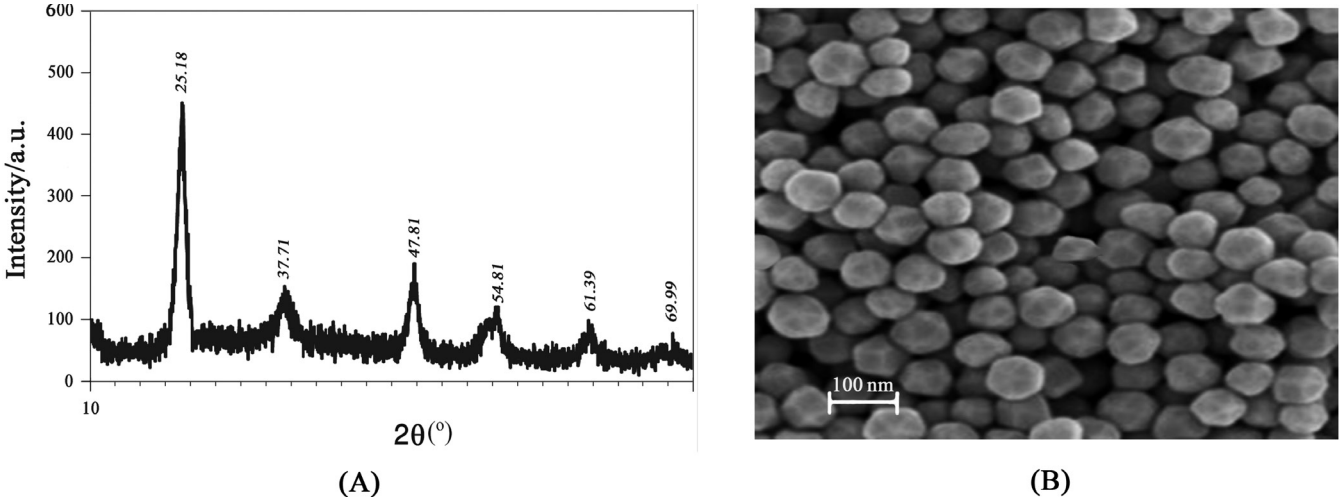


**Fig. 1** (A) X-ray diffraction pattern of $TiO_2$ nanoparticles. (B) SEM image of $TiO_2$ nanoparticles.

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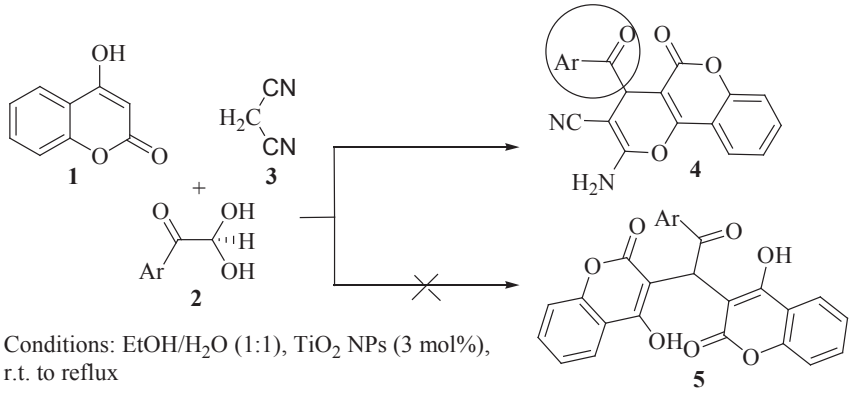



**Scheme 1** Synthesis of aroylated pyrano[3,2-c]chromene-5-ones **4** using $TiO_2$ NPs.

In order to determine the optimum amount of the catalyst, various amounts of $TiO_2$ were employed for various times in the synthesis of test compound **4a** and the results are shown in Fig. 2. As can be seen, the effect of $TiO_2$ NPs in comparison with catalyst-free and bulk cases is appreciable. Clearly, enhancing the contact between the reactants and the nanocatalyst with its high surface area had a dramatic effect.

The highest yield was obtained (80%) when the reaction was loaded with 3 mol% of the nanoparticles. As a result, the reaction mixture was stirred with catalytic amount (3 mol%) of $TiO_2$ NPs at room temperature and then heated under reflux in $EtOH/H_2O$ (1 : 1).

Having optimised the conditions, the generality of this method was investigated by the reaction of a series of aryl glyoxals with **1** and **3** in the presence of 3 mol% $TiO_2$ NPs and the results of this study are shown in Table 1. It was found that, various aryl glyoxals containing electron-donating or electron-withdrawing functional groups at different positions showed little difference in reaction time and yields of products **4b**–h (entries 2–8). Two naphthoyl analogues also gave good yields of the corresponding products **4i** and **j** (entries 9 and 10). The structures of compounds **4a**–**j** were characterised on the basis of their IR and NMR spectroscopic data and their elemental analysis. We also investigated the use of alkyl cyanoacetates instead of malononitriles **3** to synthesise the corresponding products, but there was no product formation even after 8 h under the optimised reaction conditions.

A mechanistic pathway (Scheme 2) describes a catalytic cycle for the synthesis of compounds **4a**–**j**. In the first step, a Knoevenagel condensation takes place between aryl glyoxal and malononitrile in which $TiO_2$ promotes the condensation as a versatile catalyst. In the next step, a Michael-type addition of 4-hydroxycoumarin to the corresponding aroylidene malononitriles occurs, and this is followed by an intramolecular heterocyclisation reaction leading to the formation of **4**. As can be seen, the $TiO_2$NP catalyses each of the two final steps. To investigate the reusability of $TiO_2$ Nps in synthesis of **4a**, the catalyst was recovered and reused three times and showed no appreciable loss in activity.

## Experimental

All chemicals were purchased from Merck or Aldrich. Aryl glyoxals were synthesised according to our previously reported method.[20] $TiO_2$ NPs, with a particle size of average diameter of 50 nm, were prepared according to the Alinezhad method.[15] Reaction progress was monitored by TLC (silica-gel 60 $F_{254}$, hexane/EtOAc). Mass spectra were recorded on an Agilent 5975c with a triple axis detector. IR spectra were recorded on a FT-IR JASCO-680 and the $^1$H NMR spectra were obtained on a Bruker-Instrument DPX-400 or 300 MHz Avance 2 model. The vario El CHNS was used for elemental analysis. SEM studies of the nanostructures were carried out with a JEOL JEM 3010 instrument operating at an accelerating voltage of 300 kV. X-Ray diffraction (XRD, D8, Advance, Bruker, AXS) patterns were obtained for characterisation of the heterogeneous catalyst. Melting points were measured on an electrothermal KSB1N apparatus.

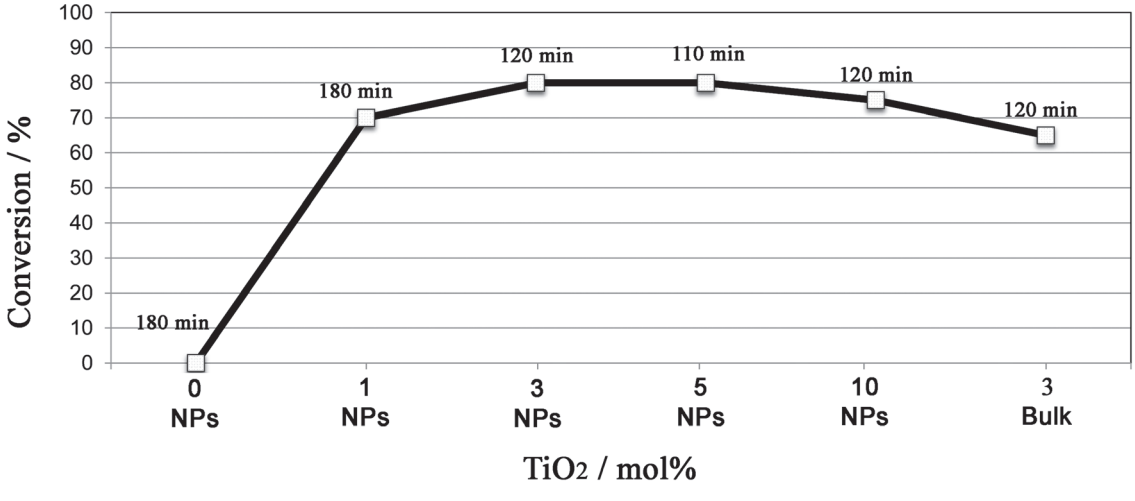
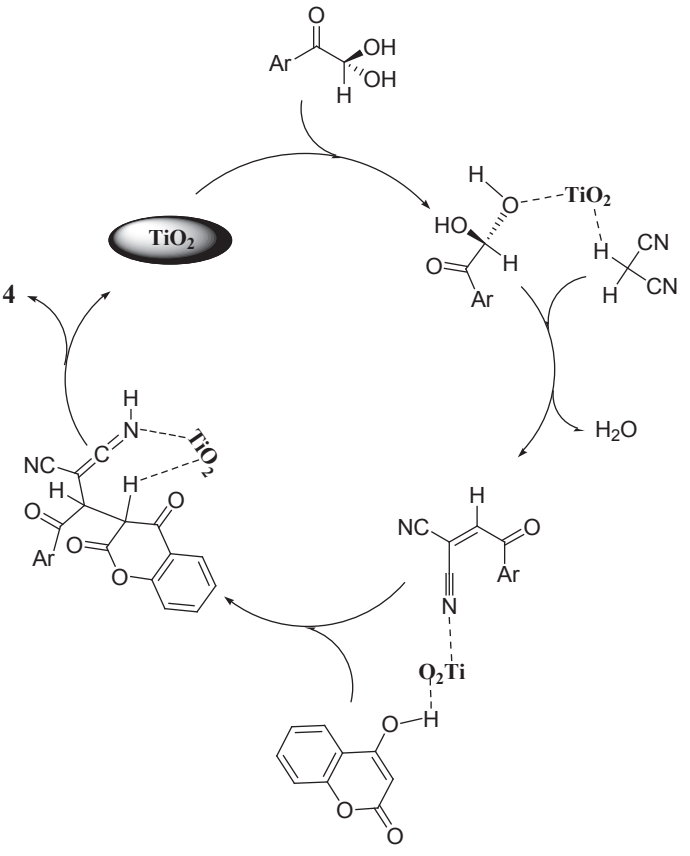



**Fig. 2** Optimisation of catalyst ($TiO_2$ nanoparticles) using the synthesis of **4a** as test compound.




**Scheme 2** Suggested mechanism for $TiO_2$-catalysed synthesis of **4.**

**Table 1** Synthesis from compounds **1**, **2a–j** and **3** of aroylated pyrano[3,2-c]chromene-5-ones **4a–j** using $TiO_2$ NPs in EtOH/$H_2O$ (Scheme 1)

| Entry | Product | Ar | Isolated yield/% | Time/min | M.p./°C |
|---|---|---|---|---|---|
| 1 | **4a** | Ph | 80 | 120 | 272–274 |
| 2 | **4b** | 4-F–Ph | 80 | 130 | 253–255 |
| 3 | **4c** | 4-Cl–Ph | 83 | 120 | 263–265 |
| 4 | **4d** | 4-Br–Ph | 85 | 110 | 263–265 |
| 5 | **4e** | 3-$NO_2$–Ph | 80 | 120 | 248–250 |
| 6 | **4f** | 4-$NO_2$–Ph | 90 | 115 | 273–275 |
| 7 | **4g** | 3-MeO–Ph | 80 | 135 | 268–270 |
| 8 | **4h** | 4-MeO–Ph | 85 | 130 | 266–268 |
| 9 | **4i** | 1-Naphthyl | 93 | 105 | 271–273 |
| 10 | **4j** | 2-Naphthyl | 95 | 100 | 278–280 |

*Preparation of $TiO_2$ nanoparticles*

Titanium tetra-*n*-butoxide (5 mL) was dissolved in absolute EtOH (5 mL) and dispersed under sonication to form a mixture, which was then added dropwise to a mixture of $HNO_3$ (65%) (1 mL), $H_2O$ (5 mL) and absolute EtOH (20 mL) under ultrasonic irradiation in a sonication cell for 15 min in order to effect the hydrolysis. After continuous sonication for 1 h, a semitransparent sol was obtained. Subsequently, the sonication was conducted so that the temperature was raised from 25 to 80 °C by the end of the reaction. The formed precipitate was filtered, washed with de-ionised water and anhydrous alcohol several times, and dried at 70 °C in the air for 12 h to produce a dry gel powder after grinding. $TiO_2$ NPs were finally obtained by calcination of the dry gel precursor at 480 °C for 2 h in air.

*Synthesis of* **4** *using $TiO_2$ NPs*

To a stirred solution of 4-hydroxycoumarin (1 mmol), aryl glyoxal (1 mmol), and malononitrile (1.2 mmol) in EtOH/$H_2O$ (1 : 1, 10 mL), $TiO_2$ NPs (0.03 mmol) was added. The mixture was stirred under reflux for 40 min. The reaction progress was monitored by TLC (hexane/AcOEt, 1 : 1). After completion of the reaction, the precipitate was filtered, dried, and dissolved in hot EtOH/THF (3 : 1) to separate the catalyst. The pure **4** was obtained after recrystallisation from EtOH/THF (3 : 1).

*2-Amino-4-benzoyl-3-cyano-4H,5H-pyrano[3,2-c]chromene-5-one* (**4a**): $^1$H NMR δ 8.16 (s, 2H, $J$=7.2 Hz), 7.90 (dd, 1H, $J_1$=8.2, $J_2$ = 1.6 Hz), 7.81–7.73 (m, 2H), 7.69 (s, 2H), 7.62 (t, 2H, $J$=8.2 Hz), 7.57–7.53 (m, 2H), 5.42 (s, 1H) ppm; $^{13}$C NMR δ 198.1, 160.0, 159.5, 154.7, 152.1, 135.3, 134.1, 133.3, 129.1, 128.8, 125.0, 122.1, 118.5, 116.8, 112.5, 101.9, 51.9, 37.1 ppm. Anal. calcd for $C_{20}H_{12}N_2O_4$: C, 69.76; H, 3.51; N, 8.14; found: C, 69.55; H, 3.41; N, 8.09%.

*2-Amino-3-cyano-4-(4'-flouro-benzoyl)-4H,5H-pyrano[3,2-c] chromene-5-one* (**4b**): $^1$H NMR δ 8.27 (m, 2H), 7.90 (dd, 1H, $J$=8.2, 1.8 Hz), 7.82–7.76 (m, 1H), 7.70 (s, 2H), 7.58–7.53 (m, 2H), 7.46 (t, 2H, $J$=8.8 Hz), 5.44 (s, 1H) ppm; $^{13}$C NMR δ 196.7, 160.0, 159.5, 154.7, 152.1, 133.3, 132.3, 132.1, 125.0, 122.1, 118.5, 116.8, 116.1, 115.8, 112.5, 101.7, 51.8, 37.1 ppm; MS (*m/z*): 362.3, 239.2, 123.1, 95.1, 75.1. Anal. calcd for $C_{20}H_{11}FN_2O_4$: C, 66.30; H, 3.06; N, 7.73; found: C, 66.37; H, 3.00; N, 7.61%.

*2-Amino-(4'-chlorobenzoyl)-3-cyano-4H,5H-pyrano[3,2-c] chromene-5-one* (**4c**): $^1$H NMR δ 8.20 (d, 2H, $J$=8.4 Hz), 7.89 (dd, 1H, $J_1$=8.2, $J_2$ = 1.4 Hz), 7.81–7.69 (m, 5H), 7.57–7.52 (m, 2H), 5.43 (s, 1H) ppm; $^{13}$C NMR δ 197.2, 160.0, 159.5, 154.7, 152.1, 139.2, 134.1, 133.3, 130.9, 129.0, 125.0, 122.1, 118.4, 116.8, 112.5, 101.6, 51.7, 37.2 ppm. Anal. calcd for $C_{20}H_{11}ClN_2O_4$: C, 63.42; H, 2.93; N, 7.40; found: C, 63.61; H, 2.99; N, 7.35%.

*2-Amino-4-(4'-bromobenzoyl)-3-cyano-4H,5H-pyrano[3,2-c] chromene-5-one* (**4d**): $^1$H NMR δ 8.10 (d, 2H, $J$=8.6 Hz), 7.91–7.76 (m, 4H), 7.71 (s, 2H), 7.58–7.53 (m, 2H), 5.42 (s, 1H) ppm; $^{13}$C NMR 197.5, 159.5, 154.7, 152.1, 134.4, 133.4, 132.0, 131.0, 125.0, 122.1, 116.8, 112.5, 101.6, 51.7, 37.2 ppm. Anal. calcd for $C_{20}H_{11}BrN_2O_4$: C, 56.76; H, 2.62; N, 6.62; found: C, 56.89; H, 2.51; N, 6.58%.

*2-Amino-3-cyano-4-(3'-nitrobenzoyl)-4H,5H-pyrano[3,2-c] chromene-5-one* (**4e**): $^1$H NMR δ 8.83 (t, 1H, $J$=1.8 Hz), 8.65 (d, 1 H, $J$=7.8 Hz), 8.61–8.57 (m, 1H), 7.98–7.89 (m, 2H), 7.82–7.77 (m, 3H),

7.59–7.53 (m, 2H), 5.57 (s, 1H) ppm; $^{13}$C NMR δ 197.0, 160.1, 159.5, 154.8, 152.1, 148.1, 136.6, 135.2, 133.5, 130.9, 128.3, 125.1, 123.1, 122.2, 118.5, 116.8, 112.5, 101.3, 51.2, 37.6 ppm. Anal. calcd for $C_{20}H_{11}N_3O_6$: C, 61.70; H, 2.85; N, 10.79; found: C, 61.88; H, 2.77; N, 10.83%.

*2-Amino-3-cyano-4-(4'-nitrobenzoyl)-4H,5H-pyrano[3,2-c] chromene-5-one* (**4f**): $^1$H NMR δ 8.46–8.38 (m, 4H), 7.90 (dd, 1H, $J$=8.2, 1.4 Hz), 7.82–7.77 (m, 3H), 7.59–7.54 (m, 2H), 5.51 (s, 1H) ppm; $^{13}$C NMR δ 197.7, 160.1, 159.5, 154.8, 152.1, 150.4, 140.2, 133.5, 130.4, 125.1, 124.0, 122.2, 116.8, 112.5, 101.3, 51.2, 37.9 ppm. Anal. calcd for $C_{20}H_{11}N_3O_6$: C, 61.70; H, 2.85; N, 10.79; found: C, 61.79; H, 2.72; N, 10.71%.

*2-Amino-3-cyano-4-(3'-methoxybenzoyl)-4H,5H-pyrano[3,2-c] chromene-5-one* (**4g**): $^1$H NMR δ =7.90 (dd, 1H, $J_1$=8.2, $J_2$=1.8 Hz), 7.815–7.75 (m, 2H), 7.70 (s, 2H), 7.62 (t, 1H, $J$=2.4 Hz), 7.57–7.52 (m, 3H), 7.32 (dd, 1H, $J_1$=7.8, $J_2$ = 2.1 Hz), 5.40 (s, 1H), 3.87 (s, 3H) ppm; $^{13}$C NMR δ 197.7, 160.0, 159.6, 159.4, 154.7, 152.1, 136.6, 133.3, 130.0, 125.0, 122.1, 121.6, 120.2, 118.5, 116.8, 113.5, 112.6, 101.9, 55.3, 52.0, 37.4 ppm. Anal. calcd for $C_{21}H_{14}N_2O_5$: C, 67.38; H, 3.77; N, 7.48; found: C, 67.48; H, 3.70; N, 7.56%.

*2-Amino-3-cyano-4-(4'-methoxybenzoyl)-4H,5H-pyrano[3,2-c] chromene-5-one* (**4h**): $^1$H NMR δ 8.15 (d, 2H, $J$=9.0 Hz), 7.89 (dd, 1H, $J_1$=8.2, $J_2$ = 1.4 Hz), 7.80–7.74 (m, 1H), 7.65 (s, 2H), 7.57–7.52 (m, 2H), 7.14 (d, 2H, $J$=9.0 Hz), 5.36 (s, 1H), 3.90 (s, 3H) ppm; $^{13}$C NMR δ 196.2, 163.9, 160.0, 159.5, 154.6, 152.0, 133.2, 131.6, 128.1, 124.9, 122.1, 118.6, 116.7, 114.1, 112.6, 102.1, 55.6, 52.2, 36.7 ppm. Anal. calcd for $C_{21}H_{14}N_2O_5$: C, 67.38; H, 3.77; N, 7.48; found: C, 67.40; H, 3.73; N, 7.40%.

*2-Amino-3-cyano-4-(1'-naphthoyl)-4H,5H-pyrano[3,2-c]chromene-5-one* (**4i**): $^1$H NMR δ 8.37 (m, 2H), 8.24 (d, 1H, $J$=8.4 Hz), 8.09–8.05 (m, 1H), 7.92 (dd, 1H, $J$=8.2, $J_2$=1.8 Hz), 7.83–7.70 (m, 4H), 7.66–7.54 (m, 4H), 5.43 (s, 1H) ppm; $^{13}$C NMR δ 200.3, 160.2, 159.6, 154.6, 152.2, 134.2, 133.4, 133.3, 133.2, 129.8, 129.0, 128.5, 128.0, 126.5, 125.1, 125.0, 124.7, 122.2, 118.3, 116.8, 112.6, 101.7, 51.4, 38.6 ppm. Anal. calcd for $C_{24}H_{14}N_2O_4$: C, 73.09; H, 3.58; N, 7.10; found: C, 73.13; H, 3.55; N, 7.01%.

*2-Amino-3-cyano-4-(2'-naphthoyl)-4H,5H-pyrano[3,2-c]chromene-5-one* (**4j**): $^1$H NMR δ 8.44 (s, 1H), 7.98–7.95 (m, 2H), 7.84–7.82 (d, 1H, $J$=8.4 Hz), 7.76–7.72 (m, 1H), 7.62–7.52 (m, 3H), 7.49–7.42 (m, 2H), 7.39 (s, 2H), 7.33 (d, 1H, $J$=7.2 Hz), 5.47 (s, 1H) ppm; $^{13}$C NMR δ 199.6, 159.5, 157.8, 153.8, 152.0, 133.2, 132.9, 130.9, 128.4, 127.4, 126.1, 126.1, 126.0, 125.8, 125.7, 124.7, 123.4, 122.4, 119.1, 116.6, 112.9, 104.6, 53.6, 37.2 ppm. Anal. calcd for $C_{24}H_{14}N_2O_4$: C, 73.09; H, 3.58; N, 7.10; found: C, 73.17; H, 3.60; N, 7.04%.

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