

## 2-Oxo-2-(arylamino)ethyl 4-formylbenzoates: Aldehyde precursors for the synthesis of new 2-amino-3-cyano-1,4-dihydropyrans

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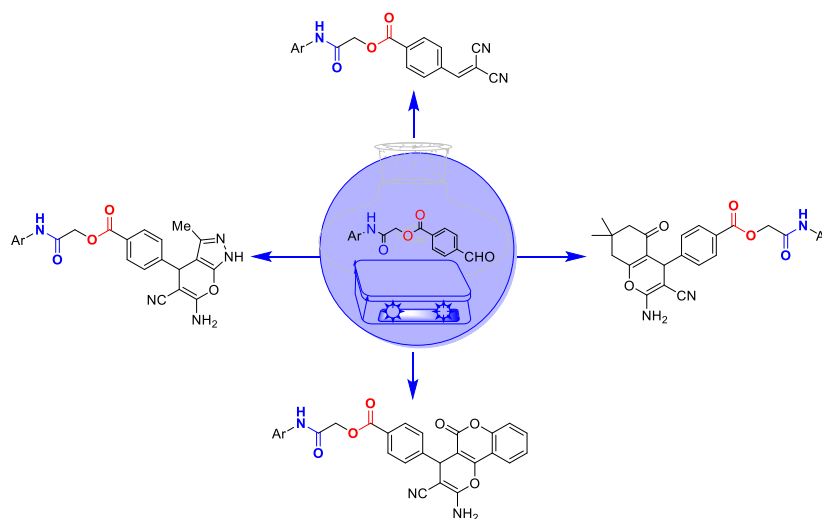
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### Abstract

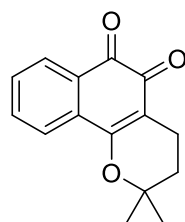
By reacting 2-chloro-*N*-aryl-acetamide with the potassium salt of *p*-formylbenzoic acid in DMF at reflux, a variety of new 2-oxo-2-(arylamino)ethyl 4-formylbenzoates were generated in good yields. The corresponding fused pyrans were obtained using a three-component reaction of the novel aldehydes with malononitrile and active methylene compounds, in particular, dimedone, pyrazolone, and 4-hydroxycoumarin, in the presence of a basic catalyst. A variety of spectra were used to confirm the structures of the new compounds.



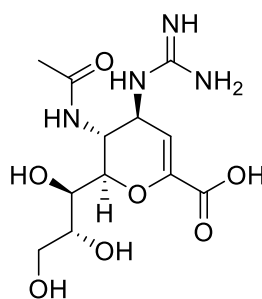
**Keywords:** Fused 1,4-dihydropyran, *N*-aryl-benzoyloxyacetamide, hybrid molecules

## Introduction

One of the most versatile structural motifs employed in medicines, material science, and natural goods is the ester. In this context, several notable natural compounds containing ester groups have been reported, including the anticancer medication quiderone and the chemotherapeutic medicine taxol for the treatment of breast and ovarian cancer. Esters are utilized as building blocks in the synthesis of organic molecules.<sup>1-4</sup> The amide motif is also the backbone of peptides and a key structural component of many natural commodities and valuable materials. A 2006 survey revealed amides in 25% of all current medications and two-thirds of therapeutic prospects. As a result, in recent years, there has been much interest in creating a synthetic approach for the production of ester and amide groups.<sup>5-7</sup> MCRs are one-pot reactions that employ three or more components to create a final product containing the majority of the atoms from all of the starting components. MCRs now outperform sequential multi-step synthesis in several ways, including operational simplicity, time and energy savings (step efficiency), high convergence rates (process efficiency), a very high bond-forming index (BFI), and high compatibility with a broad range of unprotected orthogonal functional groups. As a result, MCRs are considered a promising approach for the synthesis of highly chemo-, regio-, and stereoselective complex organic compounds with biological activity.<sup>8-17</sup> In this context, Michael reactions have garnered a great deal of attention in recent decades as effective techniques for the synthesis of novel modified derivatives, such as heterocycles and their fused analogs, from widely accessible precursors under moderate reaction conditions.<sup>18</sup> Many natural compounds have been synthesized using the heterocyclic pyran motif and its fused derivatives. They have pharmacological bioactivities ranging from antiviral to anticancer to antibacterial. The bioactive metabolite beta-lapachone I is an example of a pyran derivative with essential drug development properties (such as anticancer, antibacterial, and anti-inflammatory activity). Zanamivir II is also licensed for the treatment of influenza A and B.<sup>19-21</sup> The physiologically active heterocyclic compounds known as 1,4-DHPs are a well-known family of compounds. Furthermore, throughout the last several decades, the notion of molecular hybridization has aroused a great deal of interest in the field of drug creation. This approach creates novel hybrid compounds with better biological activity and resistance by merging two pharmacophoric moieties from separate bioactive classes.<sup>22-24</sup> In light of these findings, and our ongoing interest in using the multicomponent Michael reactions as an effective way to synthesize a variety of heterocycles,<sup>25-55</sup> we present here the design and synthesis of novel scaffolds based on fused 1,4-dihydropyran linked to benzoyloxyacetamide as new hybrid molecules, as well as results from our ongoing interest in using multicomponent Michael reactions as effective ways to synthesize a variety of heterocycles.



Beta-lapachone I

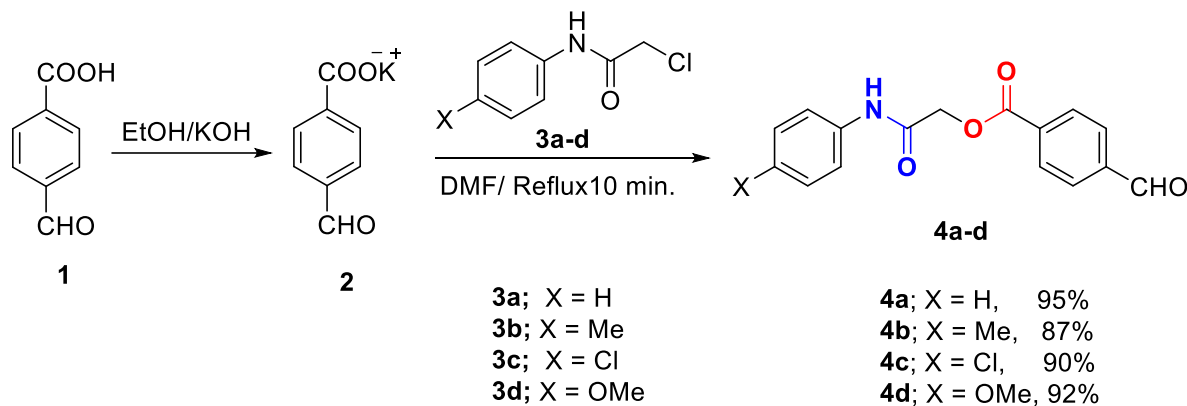


Zanamivir II

**Figure 1:** Some biologically active dihydropyran derivatives.

## Results and Discussion

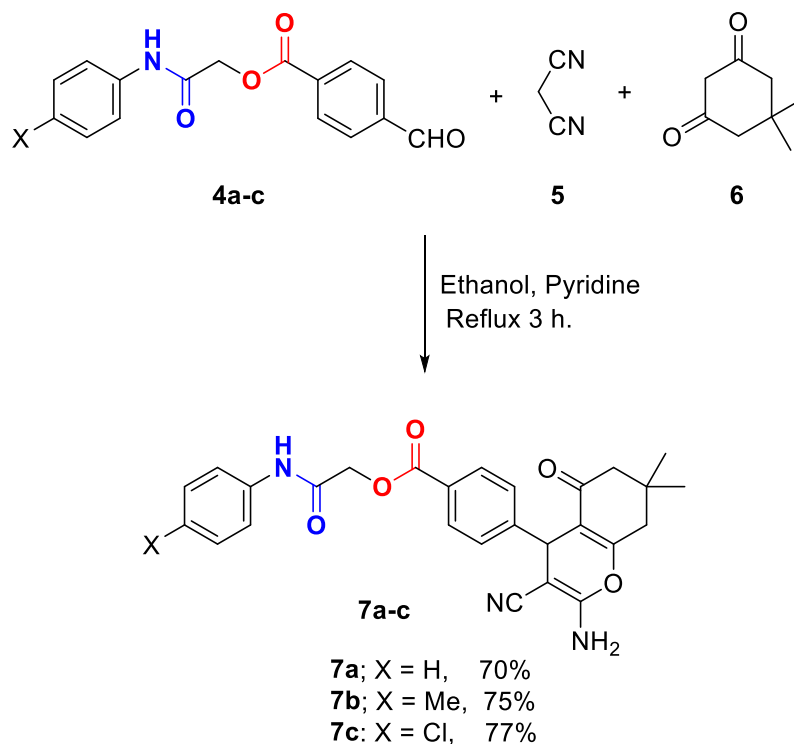
The precursors 2-oxo-2-(arylamino)ethyl 4-formylbenzoates **4a-d** were chosen for the production of the target compounds. They were made by reacting the potassium salt of *p*-formylbenzoic acid **2** with 2-chloro-*N*-arylacetamides **3a-d** in DMF at reflux (Scheme 1).



**Scheme 1:** Synthesis of 2-oxo-2-(arylamino)ethyl 4-formylbenzoate **4a-d**.

Analytical and spectroscopic methods were used to validate the structures of **4a-d**. As an example, compound **4a** showed IR bands at 3695 and 1745  $\text{cm}^{-1}$ , indicating amide NH and ester CO groups, respectively and had singlet signals corresponding to  $-\text{OCH}_2-$  and formyl protons, at 4.95 and 10.10 ppm in its  $^1\text{H}$  NMR spectrum. The mass spectrum of **4a** also revealed the correct molecular ion peak at  $m/z$  283. Following this success, the reactivity of **4** with malononitrile and various active methylene compounds was studied. In order to discover the optimal experimental reaction conditions, the reaction was carried out in the presence of a range of bases, including pyridine, piperidine, DABCO, and DBU, as well as ecologically friendly catalysts such as chitosan or montmorillonite. We also looked at how different solvents, such as EtOH,  $\text{H}_2\text{O}$ , THF, and DMF, influenced the yield of the reaction. Although all catalysts could be used, the best results were achieved in ethanol with just a modest quantity of pyridine. Using more catalysts did not increase yields, but using less, lowered yields. A solvent-free technique also generated the target chemical, but with extremely low yields. The reactions produced good yields of the products at the refluxing temperature of the solvents, but no residues of the compounds were obtained at ambient temperature even after a long period. A higher yield was obtained when the reaction time was 3-5 hours. The universality of the process and its synthetic scope were subsequently demonstrated by synthesis of a series of fused pyrans **7** and **9** under the best conditions.

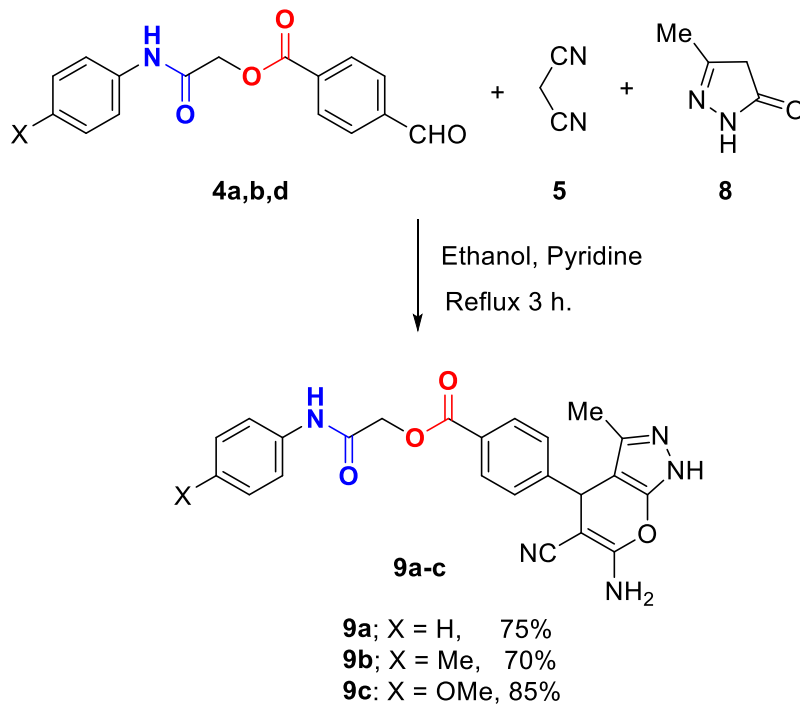
Thus, a three-component reaction of aldehyde **4a** with one equivalent of both malononitrile **5** and dimedone **6** at reflux yielded 70% yield of 2-oxo-2-(phenylamino)ethyl 4-(2-amino-3-cyano-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromen-4-yl)benzoate **7a** (Scheme 2). Under analogous circumstances, the reactions of aldehydes **4b** and **4c** with one equivalent of malononitrile **5** and dimedone **6** yielded **7b** and **7c**, respectively. Spectral data was used to validate the structures of products **7**. The absorption bands of the amino group, for example, were found in the IR spectrum of compound **7a** at 3358 and 3325  $\text{cm}^{-1}$ . It also showed the CN band at 2191  $\text{cm}^{-1}$ . The carbonyl groups appeared as broad bands at 1697 and 1666  $\text{cm}^{-1}$ , respectively. The presence of two singlet signals in the  $^1\text{H}$  NMR spectrum of **7a** at 0.95 and 1.04 ppm corresponds to the two  $\text{CH}_3$  groups. At 4.90 ppm, the chromene-H-4 signal appeared as a singlet signal. Furthermore, the  $-\text{OCH}_2$  linker was identified as a singlet signal at 4.30 ppm in its NMR spectrum.



**Scheme 2:** Synthesis of 5-oxo-5,6,7,8-tetrahydro-4*H*-chromenes **7a-c**.

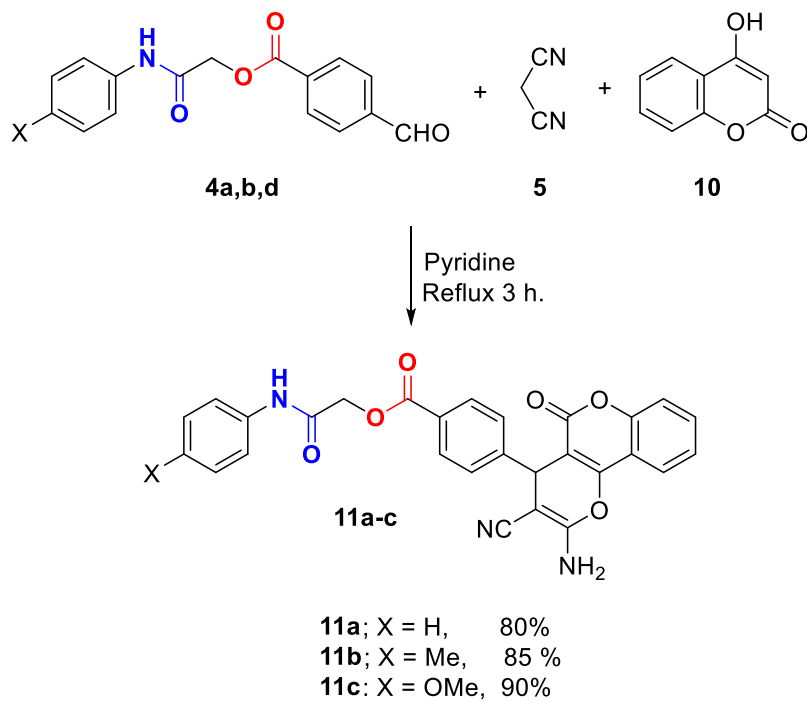
The investigation was broadened to include the synthesis of 2-oxo-2-(arylamino)ethyl 4-(6-amino-5-cyano-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazol-4-yl)benzoates **9a-c**, which was accomplished by reacting the appropriate 2-oxo-2-(arylamino)ethyl 4-formylbenzoate **4a,b,d** with one equivalent of both malononitrile **5** and pyrazolone **8** in ethanol at reflux and in the presence of pyridine as a basic catalyst. The reactions went as planned, generating **9a-c** in 70-85% yields (Scheme 3).

Compound structures were determined using spectral data. Using compound **9c** as an example, the IR spectrum revealed the presence of an amino group at 3300 and 3365  $\text{cm}^{-1}$ . The cyano group band was also revealed at 2188  $\text{cm}^{-1}$ . The presence of two singlet signals at 1.76 ppm and 3.68 ppm each integrated for three protons in the  $^1\text{H}$  NMR spectrum of **9c** was attributed to the pyrazolone  $\text{CH}_3$  and  $\text{OCH}_3$ , respectively. It also displayed a singlet signal at 4.85 ppm, which was assigned to the  $\text{CH}_2\text{O}$ - group. The singlet signal at 4.71 ppm was assigned the pyran-H-4. At 6.95 ppm, the amino group was represented by a single signal. At 10.03 ppm and 12.13 ppm, respectively, the pyrazole-NH and amide NH appeared as two broad signals.



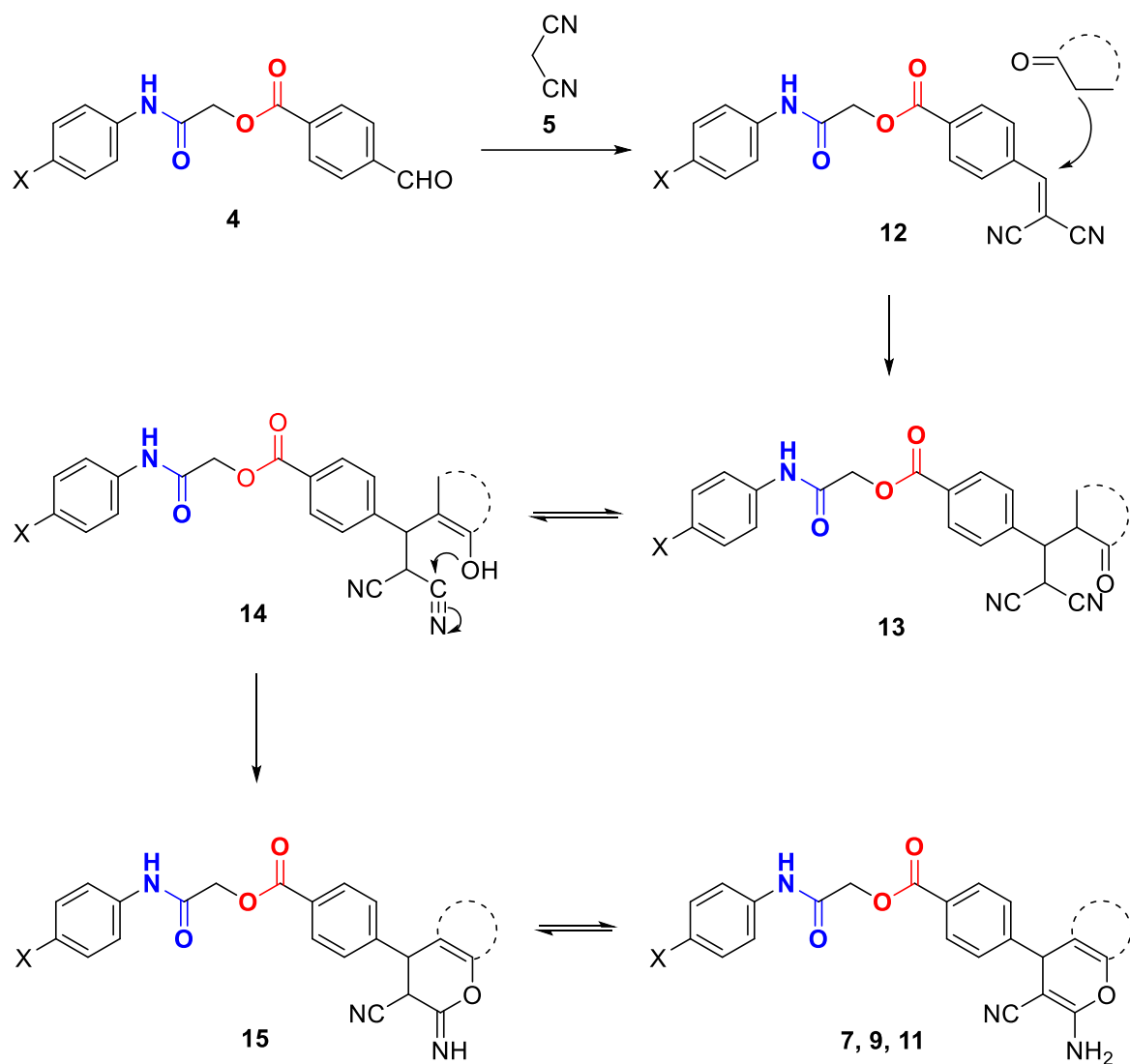
### Scheme 3: Synthesis of dihydropyrano[2,3-*c*]pyrazoles **9a-c**.

When aldehyde **4a** was mixed with one equivalent of malononitrile **5** and one equivalent of 4-hydroxy-2*H*-chromen-2-one **10** in ethanol at reflux with the presence of pyridine as a basic catalyst, only traces of the desired product **9a** were generated, even after considerable heating. Piperidine, DABCO, or DBU as basic catalysts in ethanol or 1,4-dioxane at refluxing temperatures had equivalent results. However, when the reaction was carried out in refluxing pyridine for 15 minutes, the bis(4*H*-dihydrobenzo[*b*]pyrans) **9a** were produced in 75% yield as the only product. The universality and synthetic scope were subsequently demonstrated under ideal conditions by synthesizing a series of bis(4*H*-dihydrobenzo[*b*]pyrans). Thus, a three-component reaction of aldehydes **4b** and **4d** with one equivalent of malononitrile **5** and one equivalent of 4-hydroxy-2*H*-chromen-2-one **10** in pyridine at reflux produced 2-oxo-2-(arylamino)ethyl 4-(2-amino-3-cyano-5-oxo-4,5-dihydropyrano[3,2-*c*]chromen-4-yl)benzoates **11b** and **11c** in yields ranging from 85 to 95% (Scheme 4). The composition of **11a**, for example, was validated using elemental analysis and spectral data. The presence of amino groups was confirmed by the infrared (IR) spectra, which showed bands at 3361 and 3309  $\text{cm}^{-1}$ . Furthermore, the cyano band was observed at 2198  $\text{cm}^{-1}$ . The two carbonyl groups were visible as wide bands at 1720 and 1681  $\text{cm}^{-1}$ , respectively. The pyran-H-4 was identified as a singlet signal at 4.59 ppm in the  $^1\text{H}$  NMR spectrum of **11a**. Furthermore, compound **11a** showed a singlet signal for the  $\text{OCH}_2$  protons at 4.91 ppm and the chemical shifts and integrated values of all other protons were exactly as predicted.



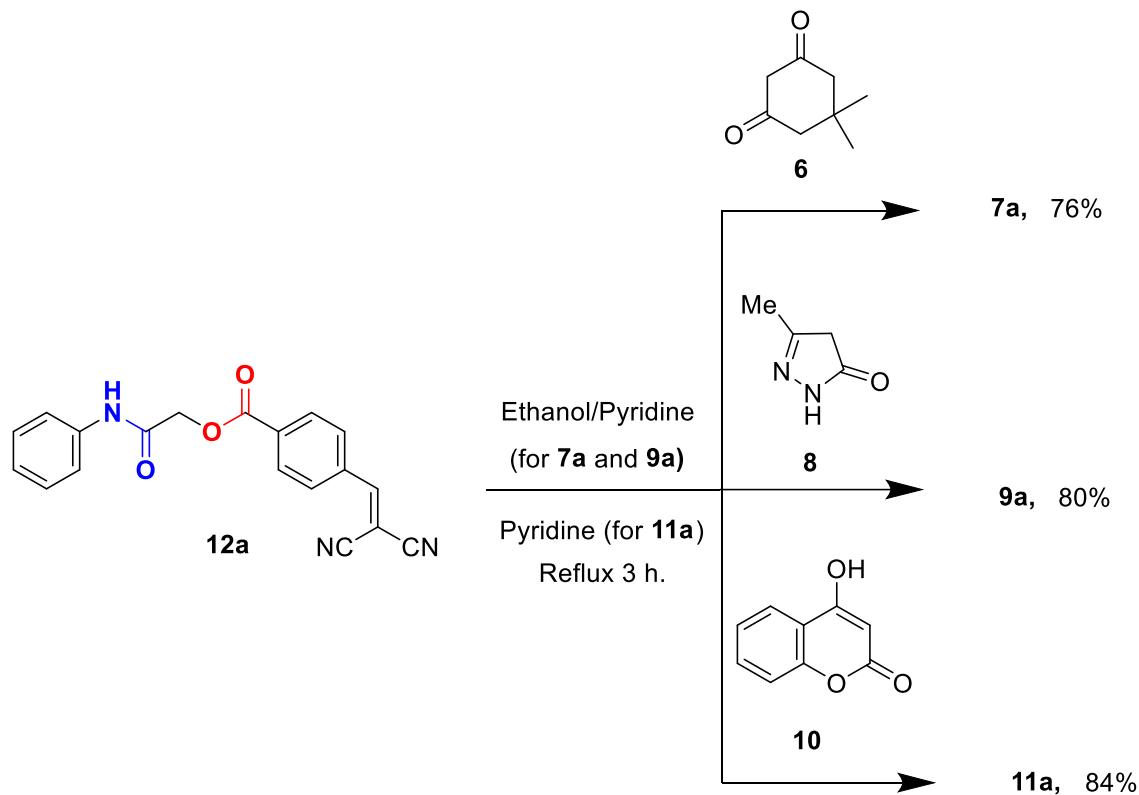
**Scheme 4:** Synthesis of dihydropyrano[3,2-c]chromenes **11a-c**.

Mechanistically, compounds **7**, **9**, and **11** may all be produced in the same way, starting with the synthesis of arylidene malonitrile derivatives **12** via condensation of aldehydes **4** with one equivalent of malononitrile **5**. The intermediate Michael adduct **13** is created by reacting **12** with one equivalent of one of the active methylene compounds, **6**, **8**, or **10**, and tautomerism then giving **14**. The target products are created via cyclic intermediates **15** produced by intramolecular cyclization of **14** (Scheme 5).



**Scheme 5:** A plausible mechanism for the formation of compounds **7**, **9** and **11**.

Through the Knoevenagel condensation of the aldehyde **4a** with one mole of malononitrile **5**, we were able to isolate an arylidenemalonitrile derivative **12a**. By treating **12a** with one mole of dimedone **6**, pyrazolone **8**, or 4-hydroxycoumarin **10**, the target compounds **7a**, **9a**, and **11a** were synthesized in high yields (Scheme 6).



**Scheme 6:** Stepwise synthesis of compounds **7a**, **9a** and **11a**.

## Conclusions

We have created a simple and fast approach for producing a wide range of new aldehydes with ester and amide substituents. We employed these novel aldehydes as precursors in three-component Michael reactions to produce a range of fused 1,4-dihydropyrans. Mild conditions, short reaction times, high efficiency, and remarkable functional group tolerance characterize the current approach. We anticipate that utilising ester and amide connections, two of the most diverse structural motifs employed in medicinal chemistry, will boost the biological activities of the ensuing fused heterocyclic systems.

## Experimental Section

**General.** Melting points were determined in open glass capillaries with a Gallenkamp apparatus. Elemental analyses were carried out at the Microanalytical Center of Cairo University, Giza, Egypt. The infrared spectra were recorded as potassium bromide disks on a Pye. Unicam SP 3–300 and Shimadzu FTIR 8101 PC infrared spectrophotometer. NMR spectra were recorded on a JEOL JNM-LA500 spectrometer, operating at 500 MHz for  $^1\text{H}$  NMR, and 125.65 MHz for  $^{13}\text{C}$  NMR. Chemical shifts were reported downfield from TMS (= 0) for  $^1\text{H}$  NMR. For  $^{13}\text{C}$  NMR, chemical shifts were reported in the scale relative to the solvent used as an internal reference. Mass spectra (EI) were obtained at 70 eV with a Shimadzu GCMQP 1000 EX spectrometer. Analytical thin layer chromatography was performed using pre-coated silica gel 60,778 plates (Fluka), and the spots were visualized with UV light at 254 nm.

### General procedure for the synthesis of aldehydes 4a-d

A mixture of *p*-formylbenzoic acid (**1**) (1 mmol) and KOH (1 mmol) in EtOH (5 mL), was heated for 10 min. Ethanol was evaporated and the produced potassium salt was dissolved in DMF (5 mL) then the 2-chloro-*N*-aryl-acetamide **3a-d** (1 mmol) was added. The reaction mixture was heated at reflux for 10 min then allowed to cool. Thereupon the mixture was poured over crushed ice and the formed precipitate was filtered off, dried, and then recrystallized from ethanol to give aldehyde **4a-d**.

**2-Oxo-2-(phenylamino)ethyl 4-formylbenzoate (4a)**. Yield (95%); colorless powder, mp 180-182 °C, IR (KBr):  $\nu$  3695 (NH), 1745 (C=O), 1720 (C=O), 1689 (C=O), 1543, 1265  $\text{cm}^{-1}$ ,  $^1\text{H}$  NMR (500 MHz, DMSO- $d_6$ ):  $\delta$  4.95 (s, 2H, OCH<sub>2</sub>), 7.07-7.56 (m, 5H, ArH), 8.05 (d, 2H, ArH, *J* 8.5 Hz), 8.20 (d, 2H, ArH, *J* 8.0 Hz), 10.10 (s, 1H, CHO), 10.24 (s, 1H, NH). MS (EI, 70 eV): *m/z* (%) 283 [ $\text{M}^+$ ], Anal. Calcd. for C<sub>16</sub>H<sub>13</sub>NO<sub>4</sub>: C, 67.84; H, 4.63; N, 4.94. Found: C, 67.72; H, 4.79; N, 4.85.

**2-Oxo-2-(*p*-tolylamino)ethyl 4-formylbenzoate (4b)**. Yield (87%); colorless powder, mp 219-221 °C, IR (KBr):  $\nu$  3749 (NH), 1705 (C=O), 1681 (C=O), 1612 (C=O), 1543, 1288  $\text{cm}^{-1}$ ,  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ ):  $\delta$  2.25 (s, 3H, CH<sub>3</sub>), 4.95 (s, 2H, OCH<sub>2</sub>), 7.12 (d, 2H, ArH, *J* 8.1 Hz), 7.46 (d, 2H, ArH, *J* 8.1 Hz), 8.08 (d, 2H, ArH, *J* 8.4 Hz), 8.23 (d, 2H, ArH, *J* 8.1 Hz), 10.13 (s, 2H, CHO & NH). MS (EI, 70 eV): *m/z* (%) 297 [ $\text{M}^+$ ], Anal. Calcd. for C<sub>17</sub>H<sub>15</sub>NO<sub>4</sub>: C, 68.68; H, 5.09; N, 4.71. Found: C, 68.45; H, 4.89; N, 4.82.

**2-((4-Chlorophenyl)amino)-2-oxoethyl 4-formylbenzoate (4c)**. Yield (90%); colorless powder, mp 193-195 °C, IR (KBr):  $\nu$  3436 (NH), 2958, 1732 (C=O), 1704 (C=O), 1671 (C=O), 1267  $\text{cm}^{-1}$ ,  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ ):  $\delta$  4.98 (s, 2H, OCH<sub>2</sub>), 7.38 (d, 2H, ArH, *J* 8.7 Hz), 7.61 (d, 2H, ArH, *J* 8.7 Hz), 8.08 (d, 2H, ArH, *J* 8.1 Hz), 8.23 (d, 2H, ArH, *J* 8.4 Hz), 10.13 (s, 1H, CHO), 10.37 (s, 1H, NH). MS (EI, 70 eV): *m/z* (%) 317 [ $\text{M}^+$ ], Anal. Calcd. for C<sub>16</sub>H<sub>12</sub>ClNO<sub>4</sub>: C, 60.49; H, 3.81; Cl, 11.16; N, 4.41. Found: C, 60.30; H, 3.99; Cl, 11.01; N, 4.50.

**2-((4-Methoxyphenyl)amino)-2-oxoethyl 4-formylbenzoate (4d)**. Yield (92%); grey crystals, mp 192-194 °C, IR (KBr):  $\nu$  3672 (NH), 3278, 1730 (C=O), 1674 (C=O), 1640 (C=O), 1550, 1257  $\text{cm}^{-1}$ ,  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ ):  $\delta$  3.72 (s, 3H, OCH<sub>3</sub>), 4.94 (s, 2H, OCH<sub>2</sub>), 6.89 (d, 2H, ArH, *J* 9.0 Hz), 7.49 (d, 2H, ArH, *J* 9.0 Hz), 8.07 (d, 2H, ArH, *J* 8.1 Hz), 8.23 (d, 2H, ArH, *J* 8.1 Hz), 10.07 (s, 1H, NH), 10.13 (s, 1H, CHO).  $^{13}\text{C}$  NMR (75 MHz, DMSO- $d_6$ ):  $\delta$  55.3, 63.6, 114.1, 121.1, 129.8, 130.3, 131.5, 134.0, 139.4, 155.6, 164.8, 164.9, 193.2. MS (EI, 70 eV): *m/z* (%) 313 [ $\text{M}^+$ ], Anal. Calcd. for C<sub>17</sub>H<sub>15</sub>NO<sub>5</sub>: C, 65.17; H, 4.83; N, 4.47. Found: C, 65.26; H, 4.70; N, 4.59.

### General procedure for the synthesis of compounds 7a-c and 9a-c

**Method A.** A mixture of aldehyde **4** (1 mmol), malononitrile **5** (1 mmol), and active methylene compound (dimedone **6** (1 mmol), or pyrazolone **8** (1 mmol)) in ethanol (15 mL) in presence of pyridine (few drops) as a basic catalyst was heated at reflux for 3 h. The formed solid was filtered off and recrystallized from the proper solvent.

**Method B.** A mixture of 2-oxo-2-(phenylamino)ethyl 4-(2,2-dicyanovinyl)benzoate **16** (1 mmol), and dimedone **6** (1 mmol) or pyrazolone **8** (1 mmol) in ethanol (15 mL) in the presence of pyridine (few drops) as a basic catalyst was heated at reflux for 3 h. The formed solid was filtered off and recrystallized from the proper solvent

**2-Oxo-2-(phenylamino)ethyl 4-(2-amino-3-cyano-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromen-4-yl)benzoate (7a)**. Yield (A; 70%, B; 76%); colorless powder (ethanol), mp 184-186 °C, IR (KBr):  $\nu$  3741 (NH), 3358 (NH<sub>2</sub>), 3325 (NH<sub>2</sub>), 2191 (C≡N), 1697 (C=O), 1666 (C=O), 1365, 1273  $\text{cm}^{-1}$ ,  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ ):  $\delta$  0.95 (s, 3H, CH<sub>3</sub>), 1.04 (s, 3H, CH<sub>3</sub>), 1.89-2.29 (m, 4H, dimedone H2, H7, H4, H5), 4.30 (s, 2H, OCH<sub>2</sub>), 4.90 (s, 1H, chromene H4), 7.06 (s, 2H, NH<sub>2</sub>), 7.28-7.59 (m, 5H, ArH), 7.88 (d, 2H, ArH, *J* 8.1 Hz), 7.96 (d, 2H, ArH, *J* 8.1 Hz), 10.17 (s, 1H, NH).  $^{13}\text{C}$  NMR (75 MHz, DMSO- $d_6$ ):  $\delta$  26.8, 28.4, 31.8, 35.7, 49.9, 57.5, 63.1, 112.2, 119.3, 119.5,

123.5, 127.6, 127.7, 128.8, 129.3, 129.7, 138.5, 150.0, 150.5, 158.6, 162.8, 165.4, 195.6. MS (EI, 70 eV):  $m/z$  (%) 471 [ $M^+$ ], Anal. Calcd. for  $C_{27}H_{25}N_3O_5$ : C, 68.78; H, 5.34; N, 8.91. Found: C, 68.65; H, 5.22; N, 9.09.

**2-Oxo-2-(*p*-tolylamino)ethyl 4-(2-amino-3-cyano-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromen-4-yl)benzoate (7b).** Yield (A; 75%); yellow powder (ethanol), mp 159-161 °C, IR (KBr):  $\nu$  3695 (NH), 3360 (NH<sub>2</sub>), 3316 (NH<sub>2</sub>), 2198 (C≡N), 1728 (C=O), 1680 (C=O), 1519 cm<sup>-1</sup>, <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  0.95 (s, 3H, CH<sub>3</sub>), 1.04 (s, 3H, CH<sub>3</sub>), 2.08-2.29 (m, 4H, dimedone H2, H7, H4, H5), 2.25 (s, 3H, CH<sub>3</sub>), 4.29 (s, 1H, chromene H4), 4.88 (s, 2H, OCH<sub>2</sub>), 7.08 (s, 2H, NH<sub>2</sub>), 7.11 (d, 2H, ArH, *J* 8.4 Hz), 7.34 (d, 2H, ArH, *J* 8.1 Hz), 7.46 (d, 2H, ArH, *J* 8.1 Hz), 7.96 (d, 2H, ArH, *J* 7.8 Hz), 10.08 (s, 1H, NH). <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  20.4, 26.8, 28.4, 31.8, 35.8, 49.9, 57.5, 63.1, 112.1, 119.4, 119.5, 124.2, 127.7, 127.7, 129.2, 129.7, 132.5, 135.9, 149.0, 150.4, 158.6, 162.8, 165.1, 195.7. MS (EI, 70 eV):  $m/z$  (%) 485 [ $M^+$ ], Anal. Calcd. for  $C_{28}H_{27}N_3O_5$ : C, 69.26; H, 5.61; N, 8.65. Found: C, 69.35; H, 5.80; N, 8.76.

**2-((4-Chlorophenyl)amino)-2-oxoethyl 4-(2-amino-3-cyano-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromen-4-yl)benzoate (7c).** Yield (A; 77%); colorless crystals (ethanol), mp 218-220 °C, IR (KBr):  $\nu$  3468 (NH), 3391 (NH<sub>2</sub>), 3323 (NH<sub>2</sub>), 2191 (C≡N), 1724 (C=O), 1686 (C=O), 1654 (C=O), 1491 cm<sup>-1</sup>, <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  0.92 (s, 3H, CH<sub>3</sub>), 1.01 (s, 3H, CH<sub>3</sub>), 2.06-2.54 (m, 4H, dimedone H2, H7, H4, H5), 4.27 (s, 1H, chromene H4), 4.88 (s, 2H, OCH<sub>2</sub>), 7.08 (s, 2H, NH<sub>2</sub>), 7.31 (d, 2H, ArH, *J* 8.0 Hz), 7.34 (d, 2H, ArH, *J* 9.0 Hz), 7.58 (d, 2H, ArH, *J* 9.0 Hz), 7.93 (d, 2H, ArH, *J* 8.5 Hz), 10.30 (s, 1H, NH). MS (EI, 70 eV):  $m/z$  (%) 505 [ $M^+$ ], Anal. Calcd. for  $C_{27}H_{24}ClN_3O_5$ : C, 64.10; H, 4.78; Cl, 7.01; N, 8.31. Found: C, 64.38; H, 4.88; Cl, 7.14; N, 8.40.

**2-Oxo-2-(phenylamino)ethyl 4-(6-amino-5-cyano-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazol-4-yl)benzoate (9a).** Yield (A; 75%, B; 80%); yellow crystals (ethanol/DMF; 3:1), mp 260-262 °C, IR (KBr):  $\nu$  3741 (NH), 3464 (NH<sub>2</sub>), 3350 (NH<sub>2</sub>), 2191 (C≡N), 1712 (C=O), 1512, 1265 cm<sup>-1</sup>, <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  1.80 (s, 3H, CH<sub>3</sub>), 4.74 (s, 1H, pyran H4), 4.91 (s, 2H, OCH<sub>2</sub>), 6.95 (s, 2H, NH<sub>2</sub>), 7.29-7.38 (m, 5H, ArH), 7.58 (d, 2H, ArH, *J* 7.8 Hz), 8.00 (d, 2H, ArH, *J* 8.4 Hz), 10.19 (s, 1H, NH), 12.15 (s, 1H, NH). <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  10.0, 36.4, 56.6, 63.2, 97.2, 119.7, 120.8, 128.0, 128.3, 129.5, 130.1, 132.8, 136.1, 150.5, 154.9, 161.3, 165.2, 165.4. MS (EI, 70 eV):  $m/z$  (%) 429 [ $M^+$ ], Anal. Calcd. for  $C_{23}H_{19}N_5O_4$ : C, 64.33; H, 4.46; N, 16.31. Found: C, 64.20; H, 4.56; N, 16.10.

**2-Oxo-2-(*p*-tolylamino)ethyl 4-(6-amino-5-cyano-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazol-4-yl)benzoate (9b).** Yield (A; 70%); orange crystals (ethanol/DMF; 3:1), mp 236-238 °C, IR (KBr):  $\nu$  3734 (NH), 3695 (NH), 3450 (NH<sub>2</sub>), 2198 (C≡N), 1728 (C=O), 1680 (C=O), 1512, 1273 cm<sup>-1</sup>, <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  1.80 (s, 3H, CH<sub>3</sub>), 2.25 (s, 3H, CH<sub>3</sub>), 4.74 (s, 1H, pyran H4), 4.89 (s, 2H, OCH<sub>2</sub>), 6.95 (s, 2H, NH<sub>2</sub>), 7.11 (d, 2H, ArH, *J* 8.4 Hz), 7.36 (d, 2H, ArH, *J* 9Hz), 7.46 (d, 2H, ArH, *J* 9Hz), 8.00 (d, 2H, ArH, *J* 8.4 Hz), 10.09 (s, 1H, NH), 12.15 (s, 1H, NH). <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  9.9, 20.6, 36.3, 56.5, 63.2, 97.1, 119.5, 120.8, 127.9, 128.1, 129.3, 130.0, 132.7, 136.0, 150.3, 154.8, 161.1, 165.1, 165.3. MS (EI, 70 eV):  $m/z$  (%) 443 [ $M^+$ ], Anal. Calcd. for  $C_{24}H_{21}N_5O_4$ : C, 65.00; H, 4.77; N, 15.79. Found: C, 65.16; H, 4.86; N, 15.68.

**2-((4-Methoxyphenyl)amino)-2-oxoethyl 4-(6-amino-5-cyano-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazol-4-yl)benzoate (9c).** Yield (A; 85%); pale yellow crystals (ethanol/DMF; 3:1), mp 228-230 °C, IR (KBr):  $\nu$  3490 (NH), 3300 (NH<sub>2</sub>), 3365 (NH<sub>2</sub>), 3260, 2188 (C≡N), 1722 (C=O), 1640 (C=O), 1405 cm<sup>-1</sup>, <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  1.77 (s, 3H, CH<sub>3</sub>), 3.69 (s, 3H, OCH<sub>3</sub>), 4.71 (s, 1H, pyran H4), 4.85 (s, 2H, OCH<sub>2</sub>), 6.85 (d, 2H, ArH, *J* 9.0 Hz), 6.95 (s, 2H, NH<sub>2</sub>), 7.33 (d, 2H, ArH, *J* 8.0 Hz), 7.46 (d, 2H, ArH, *J* 9.0 Hz), 7.98 (d, 2H, ArH, *J* 8.0 Hz), 10.03 (s, 1H, NH), 12.13 (s, 1H, NH). MS (EI, 70 eV):  $m/z$  (%) 459 [ $M^+$ ], Anal. Calcd. for  $C_{24}H_{21}N_5O_5$ : C, 62.74; H, 4.61; N, 15.24. Found: C, 62.98; H, 4.70; N, 15.36.

### General procedure for the synthesis of compounds 11a-c

**Method A.** A mixture of aldehyde **4** (1 mmol), malononitrile **5** (1 mmol), and 4-hydroxycoumarin **10** (1 mmol), in pyridine was heated at reflux for 5 h. The formed solid was filtered off and recrystallized from DMF/ethanol (3:1) to give compounds **11a-c**.

**Method B.** A mixture of 2-oxo-2-(phenylamino)ethyl 4-(2,2-dicyanovinyl)benzoate **16** (1 mmol) and 4-hydroxycoumarin **10** (1 mmol), in pyridine was heated at reflux for 3 h. The formed solid was filtered off and recrystallized from DMF/ethanol (3:1).

**2-Oxo-2-(phenylamino)ethyl 4-(2-amino-3-cyano-5-oxo-4H,5H-pyrano[3,2-c]chromen-4-yl)benzoate (11a).**

Yield (A; 80%, B; 84%); colorless powder, mp 286-288 °C, IR (KBr):  $\nu$  3695 (NH), 3361 (NH<sub>2</sub>), 3309 (NH<sub>2</sub>), 2198 (C≡N), 1720 (C=O), 1681 (C=O), 1056 cm<sup>-1</sup>, <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  4.60 (s, 1H, pyran H4), 4.91 (s, 2H, OCH<sub>2</sub>), 7.04-7.09 (m, 1H, ArH), 7.28-7.59 (m, 10H, ArH & NH<sub>2</sub>), 7.70-7.75 (m, 1H, ArH), 7.88-8.00 (m, 3H, ArH), 10.16 (s, 1H, NH). MS (EI, 70 eV): *m/z* (%) 493 [M<sup>+</sup>], Anal. Calcd. for C<sub>28</sub>H<sub>19</sub>N<sub>3</sub>O<sub>6</sub>: C, 68.15; H, 3.88; N, 8.52. Found: C, 68.30; H, 4.06; N, 8.71.

**2-Oxo-2-(*p*-tolylamino)ethyl 4-(2-amino-3-cyano-5-oxo-4H,5H-pyrano[3,2-c]chromen-4-yl)benzoate (11b).**

Yield (A; 85%); pale yellow crystals, mp 280-282 °C, IR (KBr):  $\nu$  3734 (NH), 3309 (NH<sub>2</sub>), 2198 (C≡N), 1712 (C=O), 1674 (C=O), 1612, 1527, 1273 cm<sup>-1</sup>, <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  2.25 (s, 3H, CH<sub>3</sub>), 4.59 (s, 1H, pyran H4), 4.89 (s, 2H, OCH<sub>2</sub>), 7.10 (d, 2H, ArH, *J* 8.1 Hz), 7.45-7.51 (m, 8H, ArH & NH<sub>2</sub>), 7.70-7.76 (m, 1H, ArH), 7.91-7.94 (m, 1H, ArH), 8.00 (d, 2H, ArH, *J* 8.1 Hz), 10.06 (s, 1H, NH). <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  20.5, 37.1, 57.3, 63.2, 103.3, 113.0, 116.7, 119.1, 119.4, 122.6, 124.8, 128.2, 128.3, 129.2, 129.9, 132.5, 133.2, 136.0, 149.0, 152.3, 153.8, 158.0, 159.6, 165.2, 165.3. MS (EI, 70 eV): *m/z* (%) 507 [M<sup>+</sup>], Anal. Calcd. for C<sub>29</sub>H<sub>21</sub>N<sub>3</sub>O<sub>6</sub>: C, 68.63; H, 4.17; N, 8.28. Found: C, 68.47; H, 4.30; N, 8.48.

**2-((4-Methoxyphenyl)amino)-2-oxoethyl 4-(2-amino-3-cyano-5-oxo-4H,5H-pyrano[3,2-c]chromen-4-yl)benzoate (11c).** Yield (A; 90%); grey powder, mp 277-279 °C, IR (KBr):  $\nu$  3316 (NH<sub>2</sub>), 2193 (C≡N), 1712 (C=O), 1670 (C=O), 1605, 1552, 1416 cm<sup>-1</sup>, <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  3.68 (s, 3H, OCH<sub>3</sub>), 4.56 (s, 1H, pyran H4), 4.85 (s, 2H, OCH<sub>2</sub>), 6.85 (d, 2H, ArH, *J* 9.0 Hz), 7.45-7.46 (m, 8H, ArH & NH<sub>2</sub>), 7.68-7.71 (m, 1H, ArH), 7.87-7.96 (m, 3H, ArH), 10.00 (s, 1H, NH). MS (EI, 70 eV): *m/z* (%) 523 [M<sup>+</sup>], Anal. Calcd. for C<sub>29</sub>H<sub>21</sub>N<sub>3</sub>O<sub>7</sub>: C, 66.54; H, 4.04; N, 8.03. Found: C, 66.36; H, 3.90; N, 7.87.

**2-Oxo-2-(phenylamino)ethyl 4-(2,2-dicyanovinyl)benzoate (12a).** A mixture of the aldehyde **4a** (1 mmol) and malononitrile **5** (1 mmol), in ethanol in the presence of pyridine (few drops) as a basic catalyst, was heated at reflux for 1 h. The formed solid was filtered off and recrystallized from ethanol/DMF (3:1) to give compound **16**. Yield (70%); Red crystals, mp 174-176 °C, IR (KBr):  $\nu$  3450 (NH), 3333, 2223 (C≡N), 1727 (C=O), 1687 (C=O), 1551, 1279 cm<sup>-1</sup>, <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  4.96 (s, 2H, OCH<sub>2</sub>), 7.03-7.06 (m, 1H, ArH), 7.28-7.58 (m, 4H, ArH), 8.04 (d, 2H, ArH, *J* 8.0 Hz), 8.18 (d, 2H, ArH, *J* 8.0 Hz), 8.62 (s, 1H, =CH), 10.23 (s, 1H, NH). MS (EI, 70 eV): *m/z* (%) 331 [M<sup>+</sup>], Anal. Calcd. for C<sub>19</sub>H<sub>13</sub>N<sub>3</sub>O<sub>3</sub>: C, 68.88; H, 3.95; N, 12.68. Found: C, 68.70; H, 4.16; N, 12.78.

## Supplementary Material

Copies of <sup>1</sup>H and <sup>13</sup>C NMR spectra of new compounds are given in the supplementary material associated with this manuscript

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