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Facile one-pot, three-component synthesis of novel fused 4*H*-pyrans incorporating 2-phenoxy-*N*-phenylacetamide core as novel hybrid molecules via Michael addition reaction

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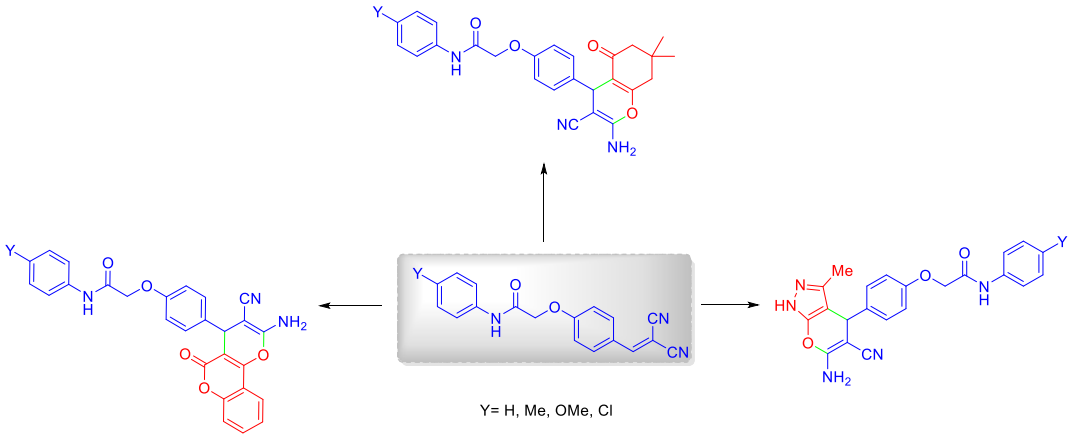
Abstract

Multitarget-directed medicines (hybrid drugs) are an effective therapeutic option for multifactorial illnesses. In this study, novel 2-phenoxy-*N*-phenylacetamide hybrids with various heterocyclic scaffolds such as 2-amino-3-cyano-4*H*-chromene, 2-amino-3-cyanopyrano[3,2-*c*]chromene, and 6-amino-5-cyano-1,4-dihydropyrano[2,3-*c*]pyrazole were efficiently synthesized. A three-component reaction of the relevant 2-(4-formylphenoxy)-*N*-(aryl)acetamide with one equivalent of malononitrile and the appropriate active methylene reagent, such as dimedone, 4-hydroxycoumarine or 3*H*-pyrazol-3-one, is used as the synthesis approach. The structures of the novel compounds were confirmed using a variety of spectra.



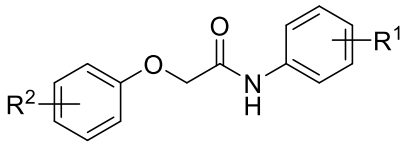
Keywords: 2-(4-Formylphenoxy)-*N*-(aryl)acetamides; malononitrile; active methylene; Michael addition; fused 4*H*-pyrans

Introduction

Multicomponent reactions, which are described as synthetic procedures that combine three or more substrates in a highly regio- and stereoselective way to generate structurally-complex organic compounds, have witnessed a remarkable increase in applications across all disciplines of organic synthesis. It is an extremely effective technique in drug discovery, and heterocyclic, and combinational chemistry.[1–7]

Molecular hybridization is a good drug-design and development technique that focuses on combining various pharmacophores to create novel, pharmacologically-active molecules. The primary objective is to boost therapeutic efficacy while reducing side effects and preventing medication resistance.[8–13] Michael addition is a well-known reaction in organic synthesis, established by Arthur Michael as one of the most advantageous techniques for the creation of mild C-C bonds. The reaction consists of the nucleophilic addition of a nucleophile to an *α*,*β*-unsaturated carbonyl molecule under basic conditions or with acidic catalysts. The Michael addition reaction has been widely explored in the synthesis of natural products and heterocyclic compounds.[14–16]

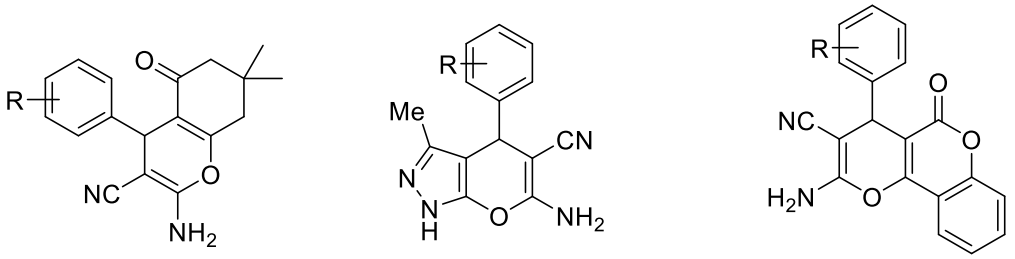
In the realm of medicinal chemistry, compounds having a 2-phenoxy-*N*-phenylacetamide core structure **1** (Fig.1) have sparked a lot of attention.[17–19] These compounds have been shown to exhibit antibacterial, antiparasitic, anticancer, and antiviral properties.[20–26]



1

Figure 1. Structure of 2-phenoxy-*N*-phenylacetamides

A range of natural and synthetic compounds having fused pyran systems was reported to have antibacterial, antiviral, anticoagulant, anti-anaphylactic, anticancer, antifungal, anticancer, antimalarial, antihyperglycemic, antidyslipidemic, diuretic, and neurodegenerative properties.[26–36] 4*H*-chromene derivatives **2**, dihydropyrano[2,3-*c*]pyrazoles **3**, and pyrano[3,2-*c*]coumarins **4** are the most well-known heterocyclic scaffolds in this respect (Fig. 2).



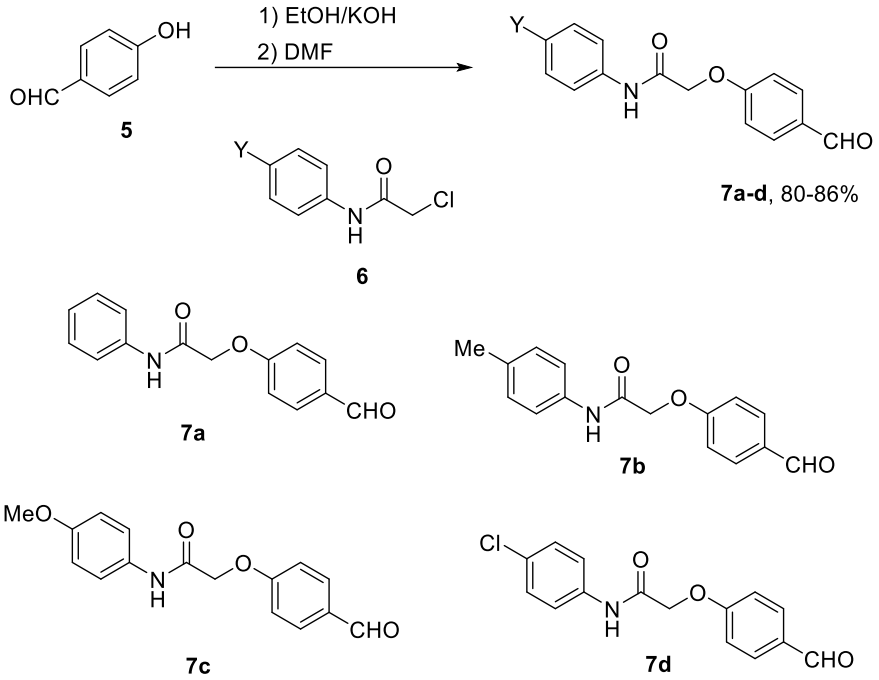
2 **3** **4**

Figure 2. Structures of 4*H*-chromenes **2**, dihydropyrano[2,3-*c*]pyrazoles **3**, and pyrano[3,2-*c*]coumarins **4**

In light of these findings, this work aimed to synthesize novel 2-phenoxy-*N*-phenylacetamide hybrids with heterocyclic scaffolds such as 2-amino-3-cyano-4*H*-chromene, 2-amino-3-cyanopyrano[3,2-*c*]chromene, and 6-amino-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile, in line with our research interests in Michael addition reactions,[37–39] and multi-component reactions.[40–44]

Results and Discussion

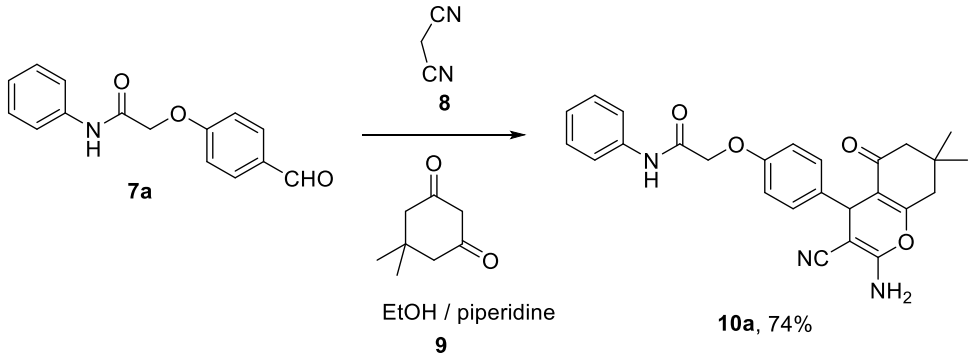
2-(4-Formylphenoxy)-*N*-(aryl)acetamides **7a-d** were selected as precursors for a variety of fused pyran systems. They were produced in 80-86% yields by reacting 2-chloro-*N*-phenylacetamide **6** with potassium salts of *p*-hydroxybenzaldehyde **5** in DMF at reflux (Scheme 1).



Scheme 1. Synthesis of 2-(4-formylphenoxy)-*N*-(aryl)acetamides **7a-d**

The structures of **7a-d** were validated by analytical and spectroscopic methods. Compound **7a** exhibited IR bands at 1680 and 1658 cm^{-1}, indicating the amide and aldehydic CO groups, respectively. In the ^{1}H NMR spectra of compound **7** derivatives, singlet signals corresponding to -OCH_2- and formyl protons were found at 4.85 and 10.17 ppm, respectively. Furthermore, the mass spectra of **7a** derivatives indicated the correct molecular ion peaks at m/z = 255.

The reactivity of **7a** with several active methylene compounds was then studied. A three-component reaction of aldehyde **7a** with one equivalent of both malononitrile **8** and dimedone **9**, in the presence of piperidine as a basic catalyst and ethanol at reflux, resulted in a good yield of 2-(4-(2-amino-3-cyano-4*H*-chromen-4-yl)phenoxy)-*N*-phenylacetamide **10a** (Scheme 2).



Scheme 2. Synthesis of (4*H*-chromen-4-yl)phenoxy-*N*-phenylacetamide **10a**

The structure of **10a** was confirmed based on spectral data. The absorption bands of the amino group were found in the IR spectrum of compound **10a** at 3410 and 3317 cm^{-1}. It also displayed the CN band at 2216 cm^{-1}. The two carbonyl groups emerged as broad bands, at 1705 and 1651 cm^{-1}, respectively. The presence of two singlet signals at 0.95 and 1.03 ppm in the ^1H NMR spectrum of **10a** corresponds to two CH_3 groups. It also revealed that chromene-H8 contains two doublets of doublets at 2.12 ppm. Chromene-H6 exhibits a singlet signal at 2.49 ppm. The chromene-H4 signal emerged as a singlet signal at 4.13 ppm. Furthermore, its NMR spectrum identified the -OCH_2 linker as a singlet signal at 4.65 ppm.

2-(4-(2-Amino-3-cyano-4*H*-chromen-4-yl)phenoxy)-*N*-phenylacetamides **10b-d** have been successfully produced in satisfactory yields in a similar way by a three-component reaction of the appropriate aldehyde **7b-d** with one equivalent of both malononitrile **8** and dimedone **9** in ethanol at reflux (Fig. 3).

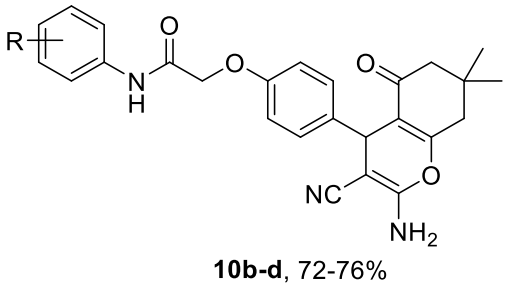
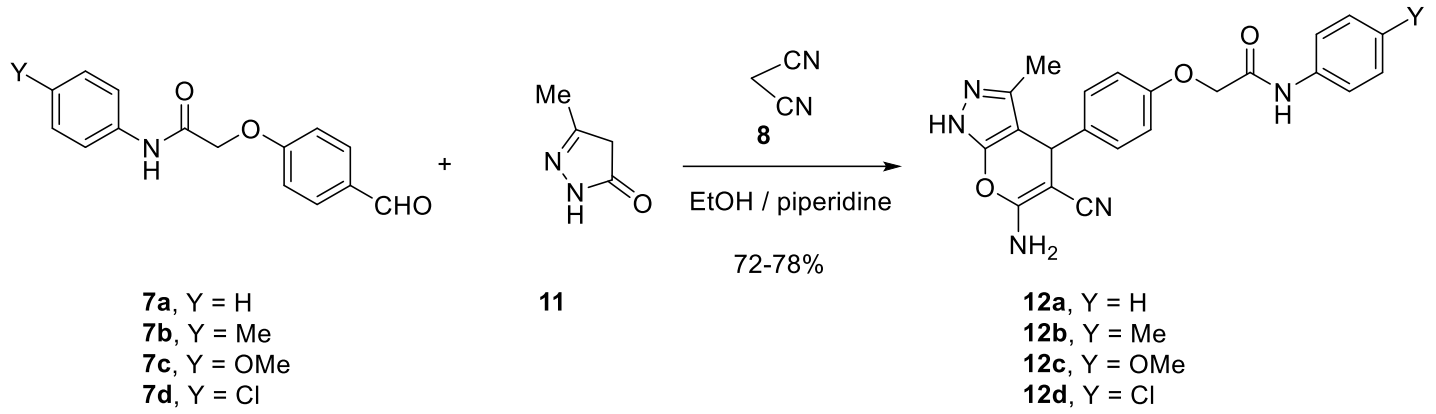


Figure 3. Structures of (4*H*-chromen-4-yl)phenoxy-*N*-phenylacetamides **10b-d**

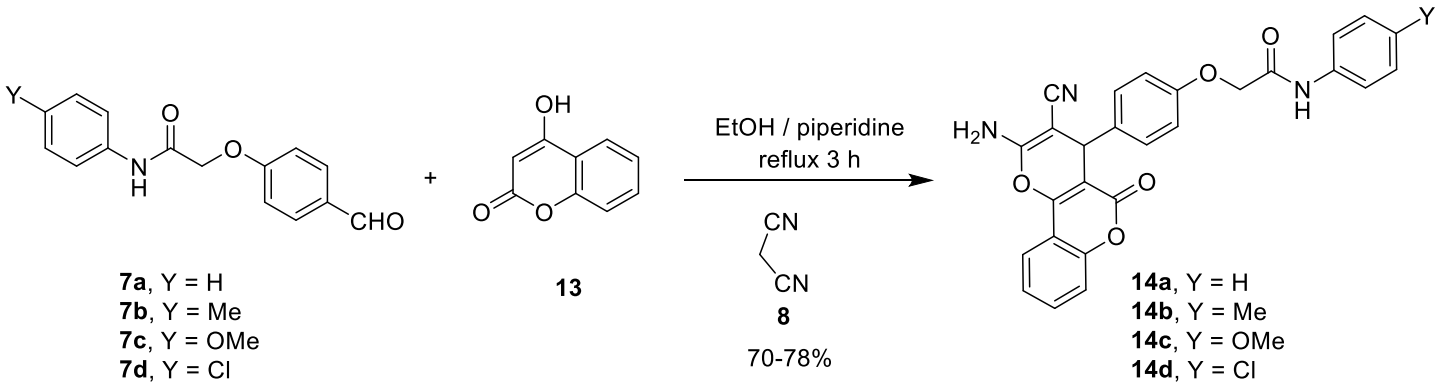
This reaction was broadened to include the synthesis of new 2-(4-(6-amino-5-cyano-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazol-4-yl)phenoxy)-*N*-phenylacetamides **12a-d** via the reaction of the appropriate 2-(4-formylphenoxy)-*N*-arylacetamides **7a-d** with one equivalent of both malononitrile **8** and pyrazolone **11** in the presence of piperidine as a basic catalyst (in refluxing ethanol). The reaction proceeded as predicted, producing **12a-d** in 72-78% yields, respectively (Scheme 3).



Scheme 3. Synthesis of (1,4-dihydropyrano[2,3-*c*]pyrazol-4-yl)phenoxy)-*N*-phenylacetamides **12a-d**

The structures of compounds **12** were established using spectral data. Using compound **12c** as an example, the IR spectrum indicated the presence of an amino group at 3479 and 3248 cm^{-1}. It also revealed the cyano-group band at 2188 cm^{-1}. The ^1H NMR spectrum of **12c** indicated the presence of two singlet signals at 1.79, and 3.72 which integrated for three protons and were ascribed to the pyrazolone CH_3 and OCH_3 hydrogens, respectively. It also showed a singlet signal at 4.62 ppm, which was attributed to -$O(CH_2)CO$- methylene hydrogens. At 4.55 ppm, the pyran-H4 was assigned to the singlet signal. The amino group was represented by a singlet signal at 6.79 ppm. The pyrazole-NH and amide NH appeared as two broad signals at 9.88 and 12.05 ppm, respectively.

Similarly, the three-component reaction of aldehydes **7a-d** with one equivalent of both malononitrile **8** and 4-hydroxy-2*H*-chromen-2-one **13** in the presence of piperidine in ethanol resulted in the production of 2-(4-(2-amino-3-cyanopyrano[3,2-*c*]chromen-4-yl)phenoxy)-*N*-phenylacetamides **14a-d** in good yields (70-78%) (Scheme 4).

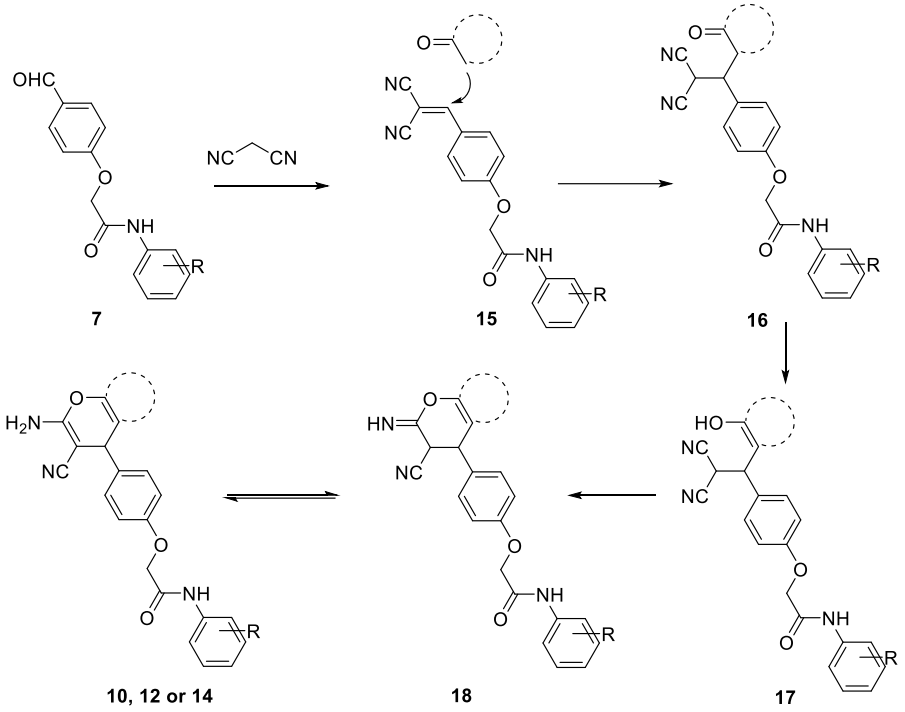


Scheme 4. Synthesis of (4*H*,5*H*-pyrano[3,2-*c*]chromen-4-yl)phenoxy-*N*-phenylacetamides **14a-d**

The constitution of compound **14a** was verified using elemental analysis and spectral data. The existence of amino groups was confirmed by the compound's infrared (IR) spectra which exhibited bands at 3466 and 3244 cm^{-1}, respectively. In addition, the cyano band was observed at 2187 cm^{-1}. The two carbonyl groups appeared as wide bands at 1712 and 1672 cm^{-1}, respectively. In the ^1H NMR spectrum of **14a**, the pyran-H4 was identified as a singlet signal at 4.41 ppm. Furthermore, compound **14a** displayed a singlet signal at 4.67

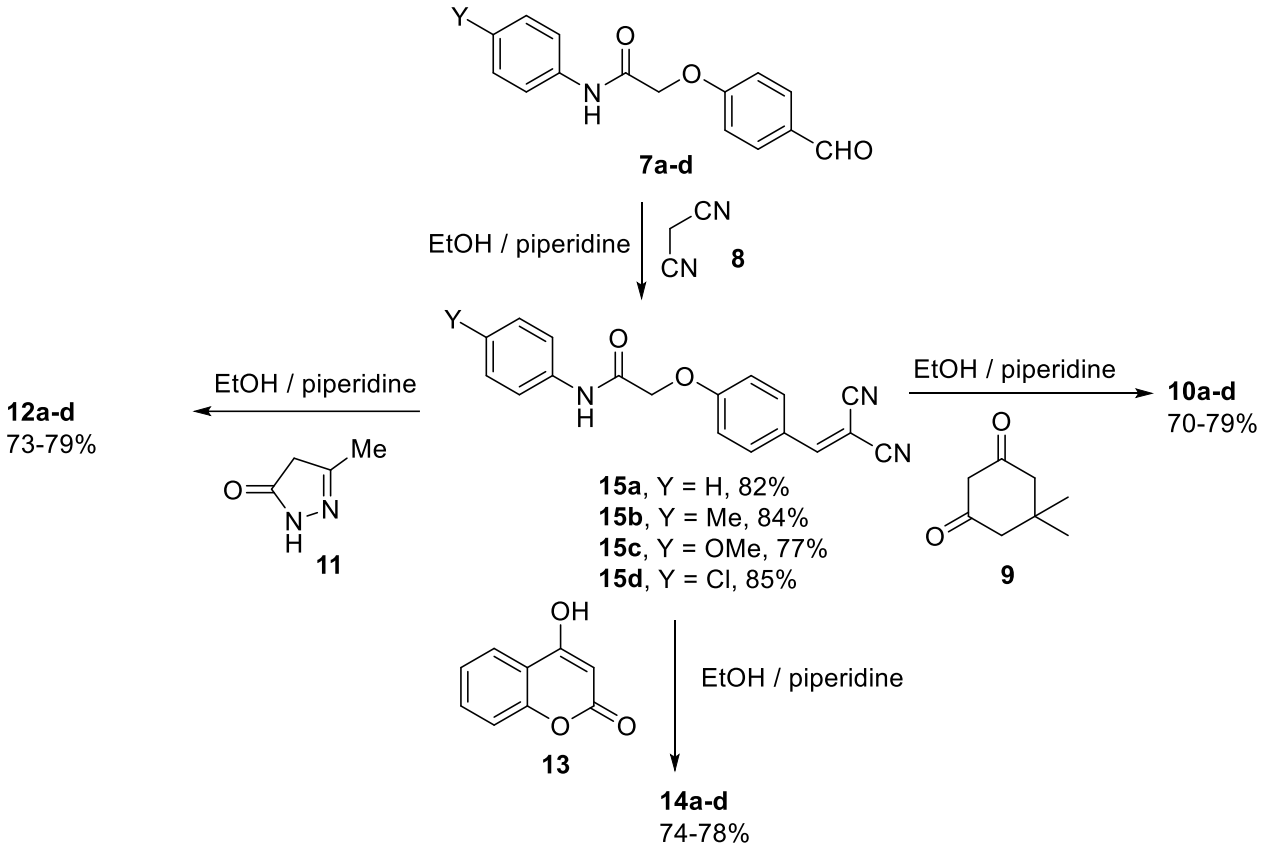
ppm, for the methylene ether bond OCH_2. All other protons' chemical shifts and integrated values were as predicted.

All of the above-mentioned processes for the synthesis of compounds **10**, **12,** and **14** may follow the same path mechanistically, which includes condensation of aldehydes **7** with one equivalent of malononitrile to create arylidene-malononitrile derivatives **15**. The intermediate Michael adducts **16** were created by reacting the latter compounds with one equivalent of one of the appropriate active methylene compounds. Tautomerization of **16** to **17**, and subsequent intramolecular cyclization, yields the cyclic intermediates **18**, which then tautomerize to yield target molecules **10**, **12** or **14**, respectively (Scheme 5).



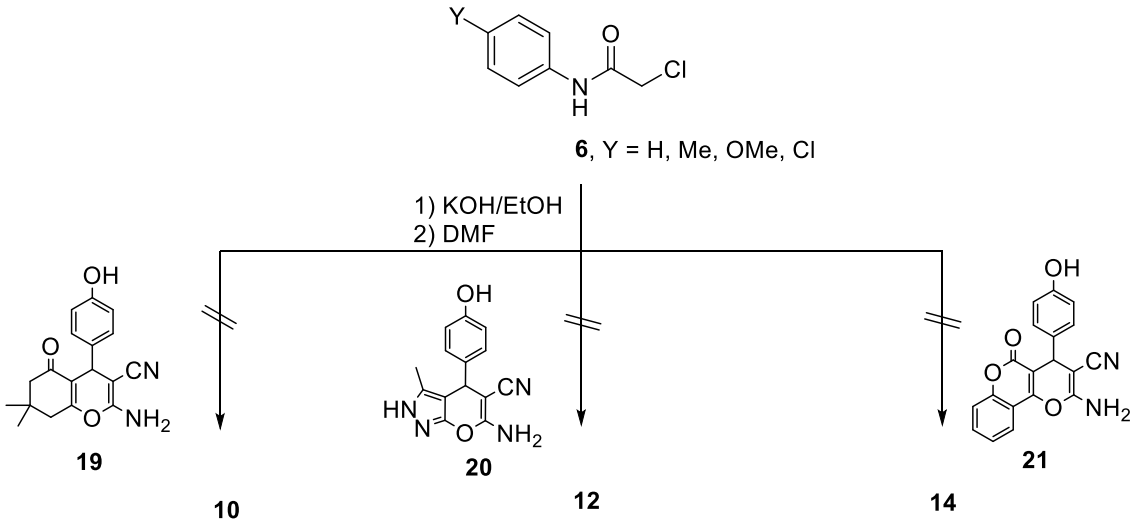
Scheme 5. A plausible mechanism for the formation of target molecules **10**, **12** or **14**

To support this proposed mechanism, we were able to isolate 2-(4-(2,2-dicyanovinyl)phenoxy)-*N*-phenylacetamide derivatives **15** by Knoevenagel condensation of the aldehydes **7** with one mole equivalent of malononitrile **8**. The target compounds **10**, **12**, and **14** were synthesized by reacting **15** with one mole of dimedone **9**, pyrazolone **11**, and 4-hydroxycoumarin **13**, respectively (Scheme 6).



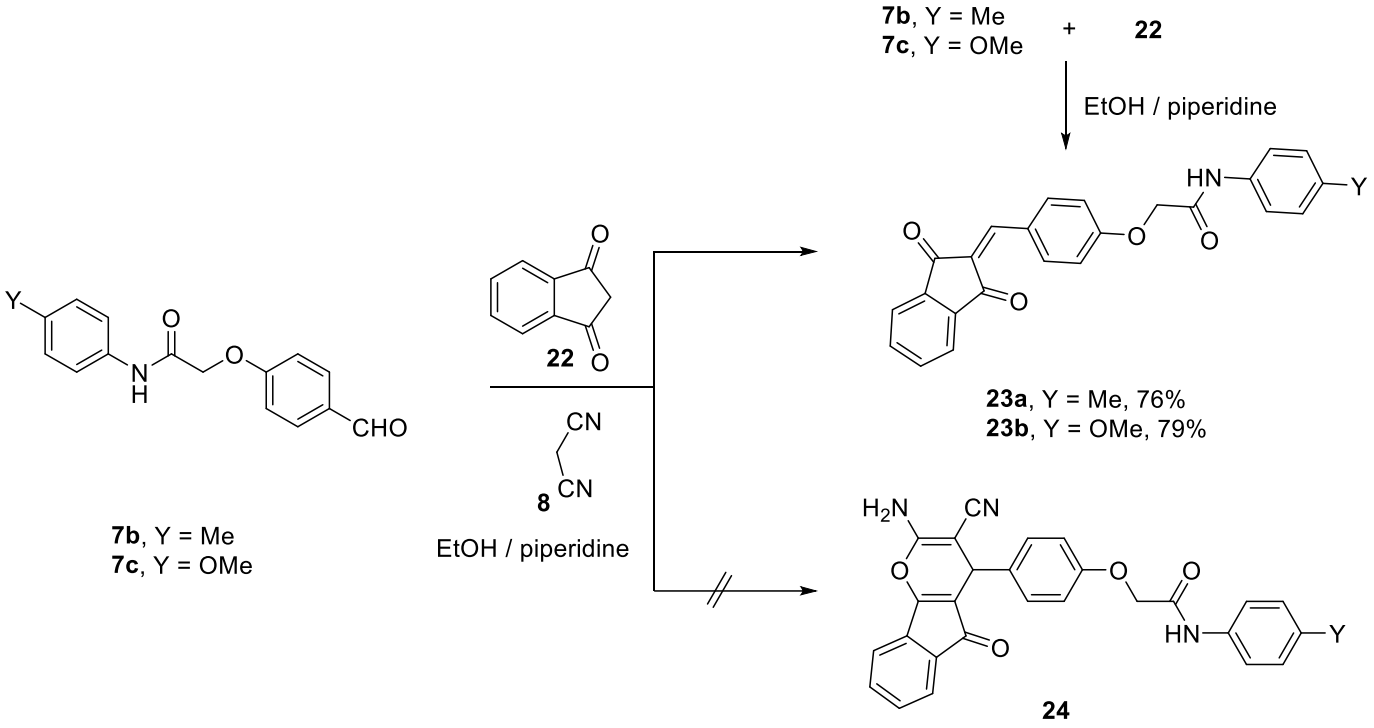
Scheme 6. Synthesis of target compounds **10**, **12**, and **14** via a two-components approach

The ^{1}H NMR spectrum of compound **15a** exhibited a singlet signal of olefinic CH protons at 8.40 ppm. Additionally, mass spectrometry validated the molecular formula of $C_{18}H_{13}N_3O_2$ by displaying the proper molecular ion peak at m/z 303. Attempts were made under various basic conditions to produce compounds **10**, **12**, and **14** by alkylation of the suitable phenols **19**[45,46], **20**[47], and **21**[48] with 2-chloro-*N*-phenylacetamide **6** (Scheme 7). Unfortunately, we were unable to separate pure samples of the target products from the reaction products due to some technical difficulties which may include competition for *N*-alkylating products.



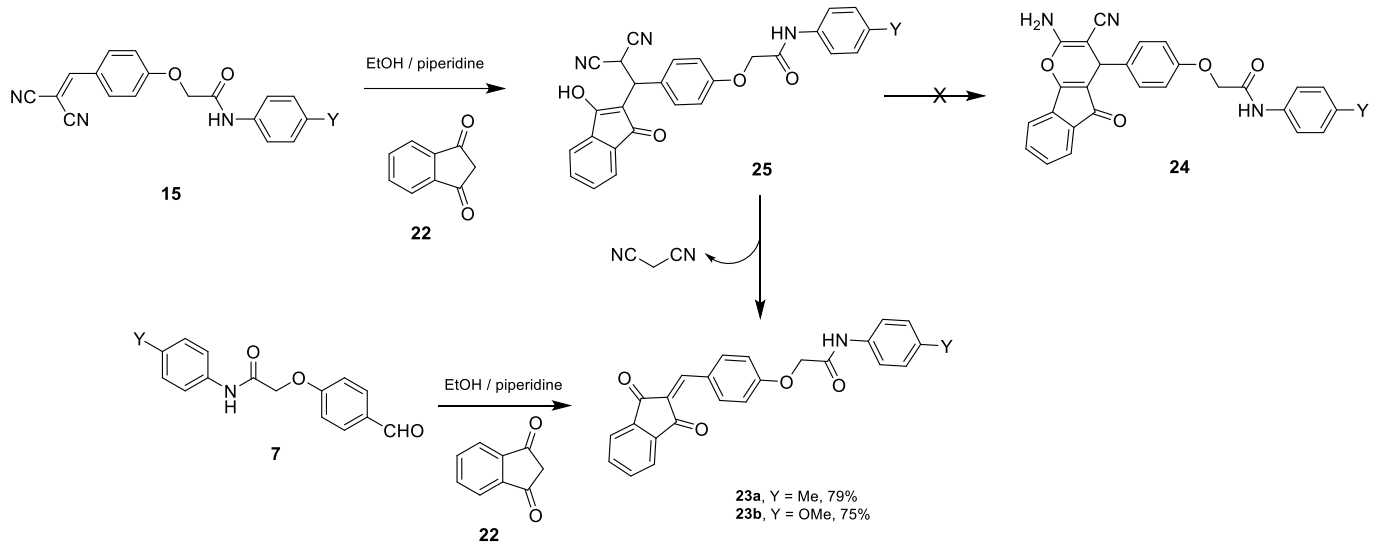
Scheme 7. Attempted synthesis of **10**, **12**, and **14** by alkylation pathway

To broaden the scope of this approach, we tried to make 2-(4-(2-amino-3-cyano-5-oxo-4,5-dihydroindeno[1,2-*b*]pyran-4-yl)phenoxy)-*N*-phenylacetamides **24** by reacting one mole equivalent of aldehydes **7** with two mole equivalents of malononitrile (**8**) and indanedione (**22**) under similar reaction conditions (Scheme 8). Unfortunately, the matching 2-(4-((1,3-dioxo-1,3-dihydro-2*H*-inden-2-ylidene)methyl)phenoxy)-*N*-phenylacetamide) **23** was generated in good yield as a single product. The latter compound's structure was further validated by comparing its physical data to an actual sample produced by condensation of one mole of the suitable aldehyde **7** with one mole of indanedione **22**.



Scheme 8. Attempted synthesis of (4,5-dihydroindeno[1,2-*b*]pyran-4-yl)phenoxy-*N*-phenylacetamides **24**

It is thought that the formation of **23** begins with the formation of the adduct **25** following treatment of **15** with **22**. After removing one mole of malononitrile, the adduct **25** decomposes to generate **23** rather than undergoing a cyclization to **24** (as depicted in Scheme 9). The compositions of **23** were determined via spectroscopic analyses. For example, the ^{1}H-NMR spectra of **23b** exhibited a singlet signal at 4.84 ppm attributed to the two –OCH_2 groups. The ylidene H-atoms were revealed as a singlet signal at 7.82 ppm. Aromatic protons were also represented by multiplets in their expected locations.



Scheme 9. A plausible mechanism for the formation of **23**

Conclusions

We have developed a simple and fast synthesis of chromenes, pyrano[3,2-*c*]pyrazoles, and pyrano[3,2-*c*]chromenes, each linked to a 2-phenoxy-*N*-phenylacetamide core, using a three-component method consisting of aldehydes, malononitrile, and the appropriate cyclic-1,3-dione. The reactions go smoothly, resulting in high yields of the required products. Attempts to synthesize these compounds *via* alkylation of the relevant phenols with 2-chloro-*N*-arylacetamide were unsuccessful.

Experimental Section

General. Melting points were measured with a Stuart melting point apparatus and were uncorrected. The IR spectra were recorded using a FTIR Bruker-vector 22 spectrophotometer as KBr pellets. The ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 as a solvent with Varian Mercury VXR-300 NMR spectrometer operating at 300 MHz and 75 MHz and Bruker AVS NMR spectrometer at 400 MHz and 100 MHz, respectively, using TMS as an internal standard. Chemical shifts were reported as δ values in ppm. Mass spectra were recorded with a Shimadzu GCMS-QP-1000 EX mass spectrometer in EI (70 eV) model. The elemental analyses were performed at the Microanalytical Center, Cairo University.

The general method for the synthesis of Compounds 7a-d.

A mixture of 4-hydroxybenzaldehyde (**5**) (1 mmol) and KOH (1 mmol) in EtOH (5 mL), was heated for 10 min. Ethanol was evaporated and the potassium salt produced was dissolved in DMF, and then 2-chloro-*N*-phenylacetamide or its derivatives (**6a-d**) (1 mmol) were added. The reaction mixture was heated for 15 min and then allowed to cool. Thereupon, the mixture was poured over crushed ice. The precipitate formed was filtered off, dried, and then recrystallized from (ethyl acetate/petroleum ether) mixture.

2-(4-Formylphenoxy)-*N*-phenylacetamide (7a). Pale yellow crystals (216 mg, 85%), Mp = 118-120ºC; IR (KBr) υ 3265 (NH), 1680 (C=O), 1658 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.85 (s, 2H, CH_2), 7.06 (t, 1H, Ar-H, *J* 7.5 Hz), 7.18 (d, 2H, Ar-H, *J* 8.7 Hz), 7.29 (t, 2H, Ar-H, *J* 7.8 Hz), 7.62 (d, 2H, Ar-H, *J* 7.8 Hz), 7.88 (d, 2H, Ar-H, *J* 8.7 Hz), 9.88 (s, 1H, NH), 10.17 (s, 1H, CHO) ppm. MS (EI, 70 eV): *m/z* (%) 255 [M^+]. Anal. Calcd for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13; N, 5.49. Found: C, 70.42; H, 5.05; N, 5.41%.

***N*-(4-Chlorophenyl)-2-(4-formylphenoxy)acetamide (7b).** Pale yellow crystals (237 mg, 82%), Mp = 160-162ºC; IR (KBr) υ 3278 (NH), 1679 (C=O), 1608 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.85 (s, 2H, CH_2), 7.18 (d, 2H, Ar-H, *J* 8.7 Hz), 7.37 (d, 2H, Ar-H, *J* 9.0 Hz), 7.66 (d, 2H, Ar-H, *J* 9.0 Hz), 7.89 (d, 2H, Ar-H, *J* 8.7 Hz), 9.88 (s, 1H, NH), 10.28 (s, 1H, CHO) ppm. MS (EI, 70 eV): *m/z* (%) 289 [M^+]. Anal. Calcd for $C_{15}H_{12}ClNO_3$: C, 62.19; H, 4.17; N, 4.83. Found: C, 61.99; H, 4.09; N, 4.67%.

2-(4-Formylphenoxy)-*N*-(*p*-tolyl)acetamide (7c). Pale brown crystals (231 mg, 86%), Mp = 128-130ºC; IR (KBr) υ 3271 (NH), 1674 (C=O), 1604 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.25 (s, 3H, CH_3), 4.82 (s, 2H, CH_2), 7.12 (d, 2H, Ar-H, *J* 8.1 Hz), 7.18 (d, 2H, Ar-H, *J* 8.4 Hz), 7.51 (d, 2H, Ar-H, *J* 8.4 Hz), 7.89 (d, 2H, Ar-H, *J* 8.4 Hz), 9.88 (s, 1H, NH), 10.05 (s, 1H, CHO) ppm. MS (EI, 70 eV): *m/z* (%) 269 [M^+]. Anal. Calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.27; H, 5.49; N, 5.10%.

2-(4-Formylphenoxy)-*N*-(4-methoxyphenyl)acetamide (7d). Gray crystals (228 mg, 80%), Mp = 138-140ºC; IR (KBr) υ 3268 (NH), 1669 (C=O), 1600 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.72 (s, 3H, O-CH_3), 4.81 (s, 2H, CH_2), 6.89 (d, 2H, Ar-H, *J* 9.0 Hz), 7.18 (d, 2H, Ar-H, *J* 8.7 Hz), 7.53 (d, 2H, Ar-H, *J* 9.0 Hz), 7.89 (d, 2H, Ar-H, *J* 8.7 Hz), 9.88 (s, 1H, NH), 10.04 (s, 1H, CHO) ppm. MS (EI, 70 eV): *m/z* (%) 285 [M^+]. Anal. Calcd for $C_{16}H_{15}NO_4$: C, 67.36; H, 5.30; N, 4.91. Found: C, 67.20; H, 5.16; N, 4.80%.

General Procedure for synthesis of compounds 10a-d, 12a-d, 14a-d, and 23

Methods A. A mixture of 2-(4-formylphenoxy)-*N*-(aryl)acetamides **7a-d**, malononitrile **8**, and the active methylene reagent (dimedone, dimedone **9**, pyrazolone **11**, 4-hydroxy-2*H*-chromen-2-one **13**, or indanedione **22**) (1 mmol) in ethanol (15 mL) was heated at reflux in presence of piperidine (0.2 mL). The crude solid was isolated and recrystallized from the proper solvent, dried, and reused in another reaction.

Methods B. A mixture of 2-(4-(2,2-dicyanovinyl)phenoxy)-*N*-arylacetamide derivatives **15a-d**, and the active methylene reagent (dimedone **9**, pyrazolone **11**, 4-hydroxy-2*H*-chromen-2-one **13** or indanedione **22**) in absolute ethanol (15 mL) was heated at reflux in the presence of piperidine (0.2 mL). The crude solid was isolated and recrystallized from the proper solvent, dried, and reused in another reaction.

2-(4-(2-Amino-3-cyano-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromen-4-yl)phenoxy)-*N*-phenylacetamide (10a). Was obtained as a white solid (ethanol-dioxane (1:1)), (method A, 328 mg, 74%; method B, 319 mg, 72%), mp 218–220ºC; IR (KBr): ν max: 3410, 3317 (NH_2 and NH), 2216 (CN) and 1705,1651 (2CO) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d6): δ, ppm: 0.95 (s, 3H, CH_3), 1.03 (s, 3H, CH_3), 2.12 (dd, 2H, H8,), 2.49 (s, 2H, H6), 4.13 (s, 1H, pyrane-H4), 4.65 (s, 2H, -OCH_2CO-), 6.89-7.65 (m, 11H , Ar-H+NH_2), 10.02 (s, 1H, NH), ^{13}C NMR (75 MHz, DMSO-d6): δ, ppm: 18.5, 26.8, 28.3, 31.7, 34.8, 50.0, 58.6, 67.2, 112.9, 114.4, 119.7, 123.7, 128.2, 128.6, 137.6, 138.3, 156.5, 158.4, 162.2, 166.6, 195.6; MS (EI): m/z (%) = 443 (M^+). Anal. Calcd. for $C_{26}H_{25}N_3O_4$ (443.50): C, 70.41; H, 5.68; N, 9.47. Found: C, 70.60; H, 5.88; N, 9.67.

2-(4-(2-Amino-3-cyano-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromen-4-yl)phenoxy)-*N*-(*p*-tolyl)acetamide (10b). Was obtained as a white solid (ethanol-dioxane (1:1)), mp 226–228ºC, (method A, 329 mg, 72%; method B, 356 mg, 78%); IR (KBr): ν max: : 3447,3336 (NH_2), 2189 (CN), 1689 and 1651 (2CO) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d6): δ, ppm: : 0.94 (s, 3H, CH_3), 1.03 (s, 3H, CH_3), 2.12 (dd, 2H, H8), 2.25 (s, 3H, CH_3) , 2.49 (s, 2H, H6), 4.13 (s, 1H, pyrane-H4), 4.62 (s, 2H, -OCH_2CO-) , 6.89-7.52 (m, 10H, Ar-H+NH_2), 9.9 (s, 1H,

NH) ; MS (EI): m/z (%) = 457 (M^+). Anal. Calcd. for $C_{27}H_{27}N_3O_4$ (457.53): C, 70.88; H, 5.95; N, 9.18; Found: C, 70.98; H, 6.05; N, 9.38.

2-(4-(2-Amino-3-cyano-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromen-4-yl)phenoxy)-*N*-(4-methoxyphenyl)acetamide (10c). Was obtained as a white solid (ethanol-dioxane (1:1)), mp 174–176°C; (method A, 359 mg, 76%; method B, 331 mg, 70%); IR (KBr): ν max: 3403 , 3366 (NH_2), 2181 (CN), 1689 and 1651 (2CO) cm^{-1} ; ^1H NMR (300 MHz, DMSO-d6): *δ*, ppm: 0.95 (s, 3H, CH_3), 1.03 (s, 3H, CH_3), 2.12 (dd, 2H, H8), 2.49 (s, 2H, H6), 3.7 (s, 3H, -OCH_3-), 4.13 (s, 1H, pyrane-H4), 4.61 (s, 2H, -OCH_2CO-), 6.87-7.54 (m, 10H , Ar-H+NH_2), 9.8 (s, 1H, NH) ; MS (EI): m/z (%) = 473 (M^+). Anal. Calcd. for $C_{27}H_{27}N_3O_5$ (473.53): C, 68.49; H, 5.75; N, 8.87; Found: C, 68.68; H, 5.98; N, 8.73.

2-(4-(2-Amino-3-cyano-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromen-4-yl)phenoxy)-*N*-(4-chlorophenyl)acetamide (10d). Was obtained as a white solid (ethanol-dioxane (1:1)), mp 246–248°C; (method A, 362 mg, 76%; method B, 377 mg, 79%), IR (KBr): ν max: 3402 , 3356 (NH_2), 2183 (CN), 1689 and 1651 (2CO) cm^{-1}; ^1H NMR (300 MHz, DMSO-d6): *δ*, ppm: 0.94 (s, 3H, CH_3), 1.03 (s, 3H, CH_3), 2.12 (dd, 2H, H8), 2.49 (s, 2H, H6), 4.13 (s, 1H, pyrane-H4), 4.65 (s, 2H, -OCH_2CO-), 6.89-7.65 (m, 10H, Ar-H+NH_2), 10.16 (s, 1H, NH) ; MS (EI): m/z (%) = 477 (M^+). Anal. Calcd. for $C_{26}H_{24}ClN_3O_4$ (477.95): C, 65.34; H, 5.06; N, 8.79; Found: C, 65.63; H, 5.33; N, 9.11.

2-(4-(6-Amino-5-cyano-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazol-4-yl)phenoxy)-*N*-phenylacetamide (12a). Was obtained as a white solid (ethanol-dioxane (1:1)), mp 242-244°C; (method A, 289 mg, 72%; method B, 309 mg, 77%), IR (KBr): ν max: 3477, 3333 (NH_2 and 2NH), 2221 (CN), 1691 and 1623 (2CO) cm^{-1}, ^1H NMR (300 MHz, DMSO-d6): *δ*, ppm: 1.78 (s, 3H, CH_3) , 4.55 (s, 1H, pyrane-H4), 4.66 (s, 2H, CH_2), 6.79 (br s, 2H, NH_2), 6.965 (d, 2H, Ar-H, *J*8.1 Hz), 7.05-7.34 (m, 5H, Ar-H), 7.61-7.64 (d, 2H, Ar-H, *J* 8.1 Hz) 10.02 (s, 1H, NH), 12.05 (s, 1H, NH) ; MS (EI): m/z (%) = 401 (M^+). Anal. Calcd. for $C_{22}H_{19}N_5O_3$ (401.43): C, 65.83; H, 4.77; N, 17.45; Found: C, 66.11; H, 4.59; N, 17.23.

2-(4-(6-Amino-5-cyano-3-methyl-1,4-dihydropyrano[2,3-c]pyrazol-4-yl)phenoxy)-*N*-(*p*-tolyl)acetamide (12b). Was obtained as a white solid (ethanol-dioxane (1:1)), mp 240-242°C; (method A, 324 mg, 78%; method B, 303 mg, 73%), IR (KBr): ν max: 3487, 3394 (NH_2 and 2NH), 2196 (CN), 1681 and 1642 (2 C=O) cm^{-1}, ^1H NMR (300 MHz, DMSO-d6): *δ*, ppm: 1.78 (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 4.54 (s, 1H, pyrane-H4), 4.63 (s, 2H, CH_2), 6.78 (br s, 2H, NH_2), 6.96 (d, 2H, Ar-H, *J*8.4 Hz), 7.08-7.13 (m, 4H, Ar-H), 7.52 (d, 2H, Ar-H, *J* 8.4 Hz), 9.9 (s, 1H, NH), 12.05 (s, 1H, NH) ;MS (EI): m/z (%) = 415 (M^+). Anal. Calcd. for $C_{23}H_{21}N_5O_3$ (415.45): C, 66.49; H, 5.10; N, 16.86; Found: C, 66.71; H, 5.33; N, 17.02,

2-(4-(6-Amino-5-cyano-3-methyl-1,4-dihydropyrano[2,3-c]pyrazol-4-yl)phenoxy)-*N*-(4-methoxyphenyl)-acetamide (12c). Was obtained as a white solid (ethanol-dioxane (1:1)), mp 240-242°C; (method A, 332 mg, 77%; method B, 315 mg, 73%), IR (KBr): ν max : 3479, 3248 (NH_2 and 2NH), 2188 (CN), 1667 and 1647 (2 C=O) cm^{-1}; ^1H NMR (300 MHz, DMSO-d6): *δ*, ppm: 1.79 (s, 3H, CH_3), 3.72 (s, 3H, -OCH_3-), 4.55 (s, 1H, pyrane-H4), 4.62 (s, 2H, CH_2), 6.79 (br s, 2H, NH_2), 6.87-6.97 (m, 4H, Ar-H), 7.09 (d, 2H, Ar-H, *J* 8.7 Hz), 7.52 (d, 2H, Ar-H, *J* 8.7 Hz) 9.88 (s, 1H, NH), 12.05 (s, 1H, NH), ^{13}C NMR (75 MHz, DMSO-d6): *δ*, ppm: 9.8, 35.5, 55.2, 57.5, 67.2, 97.8, 113.8, 114.6, 120.6, 120.8, 121.4, 128.5, 131.4, 135.5, 137.2, 155.5, 156.6, 160.7, 166.1; MS (EI): m/z (%) = 431 (M^+). Anal. Calcd. for $C_{23}H_{21}N_5O_4$ (431.45): C, 64.03; H, 4.91; N, 16.31; Found: C, 64.26; H, 5.12; N, 16.43

2-(4-(6-Amino-5-cyano-3-methyl-1,4-dihydropyrano[2,3-c]pyrazol-4-yl)phenoxy)-*N*-(4-chlorophenyl)-acetamide (12d). Was obtained as a white solid (ethanol-dioxane (1:1)), mp 232-234°C; (method A, 339 mg, 78%; method B, 344 mg, 79%), IR (KBr): ν max : 3466, 3238 (NH_2 and 2NH), 2223 (CN), 1654 and 1643 (2CO) cm^{-1}; ^1H NMR (300 MHz, DMSO-d6): *δ*, ppm: 1.78 (s, 3H, CH_3), 4.55 (s, 1H, pyrane-H4), 4.66 (s, 2H, CH_2), 6.79 (br s, 2H, NH_2), 6.96 (d, 2H, Ar-H, J=9 Hz), 7.12 (d, 2H, Ar-H, *J* 9Hz), 7.38 (d, 2H, Ar-H, *J* 9Hz), 7.69 (d, 2H, Ar-H, *J*

9Hz), 10.1 (s, 1H, NH), 12.05 (s, 1H, NH), ^{13}CNMR (75 MHz,DMSO-d6): *δ*, ppm: 9.7, 35.3, 57.5, 66.9, 97.8, 114.5, 121.5, 127.5, 128.6, 128.7, 135.9, 137.0, 137.2, 154.6, 156.4, 159.8, 166.9; MS (EI): m/z (%) = 435 (M^+). Anal. Calcd. for $C_{22}H_{18}ClN_5O_3$ (435.87): C, 60.62; H, 4.16; N, 16.07; Found: C, 60.88; H, 4.34; N, 16.29.

2-(4-(2-Amino-3-cyano-5-oxo-4*H*,5*H*-pyrano[3,2-*c*]chromen-4-yl)phenoxy)-*N*-phenylacetamide (14a). Was obtained as a white solid (ethanol-dioxane (1:1)), mp 264-266^{o}C; (method A, 344 mg, 74%; method B, 363 mg, 78%) ; IR (KBr): ν max: 3466, 3244 (NH_2 and NH), 2187 (CN), 1712 and 1672 (2CO) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d6): *δ*, ppm: 4.41 (s, 1H, pyrane H4), 4.67 (s, 2H, -OCH_2CO-), 6.96 (br s, 2H, NH_2) 7.06-7.68 (m, 11H, Ar-H), 7.91 (d, 2H, Ar-H, *J*7.8HZ), 10.03 (s, 1H, NH) ; MS (EI): m/z (%) = 465 (M^+). Anal. Calcd. for $C_{27}H_{19}N_3O_5$ (465.47): C, 69.67; H, 4.11; N, 9.03; Found: C, 69.83; H, 4.32; N, 9.22.

2-(4-(2-Amino-3-cyano-5-oxo-4*H*,5*H*-pyrano[3,2-c]chromen-4-yl)phenoxy)-*N*-(*p*-tolyl)acetamide (14b). Was obtained as a white solid (ethanol-dioxane (1:1)), mp 244-246^{o}C; (method A, 335 mg, 70%; method B, 354 mg, 74%), IR (KBr): ν max: 3435, 3297 (NH_2 and NH), 2225 (CN), 1712 and 1658 (2CO) cm^{-1}, ^{1} H NMR (300 MHz, DMSO-d6): *δ*, ppm: 2.24 (s, 3H, CH_3), 4.41 (s, 1H, pyrane H4), 4.63 (s, 2H, -OCH_2CO-), 6.95 (br s, 2H, NH_2), 7.12 (d, 2H, Ar-H, *J* 8.4 Hz), 7.21 (d, 2H, Ar-H, *J*8.4 Hz), 7.33-7.7 (m, 6H, Ar-H), 7.91 (d, 2H, Ar-H, *J* 8.4Hz), 9.9 (s, 1H, NH) ; MS (EI): m/z (%) = 479(M^+). Anal. Calcd. for $C_{28}H_{21}N_3O_5$ (479.49): C, 70.14; H, 4.41; N, 8.76; Found: C, 70.37; H, 4.73; N, 8.98.

2-(4-(2-Amino-3-cyano-5-oxo-4*H*,5*H*-pyrano[3,2-*c*]chromen-4-yl)phenoxy)-*N*-(4-methoxyphenyl)acetamide (14c). Was obtained as a white solid (ethanol-dioxane (1:1)), mp 240-242^{o}C; (method A, 386 mg, 78%; method B, 381 mg, 77%), IR (KBr): ν max: 3448, 3274 (NH_2 and NH), 2198 (CN), 1730 and 1654 (2CO) cm^{-1} , ^{1}H NMR (300 MHz, DMSO-d6): *δ*, ppm: 3.71 (s, 3H, -OCH_3-), 4.41 (s, 1H, pyrane- H4), 4.62 (s, 2H, -OCH_2CO-), 6.88 (d, 2H, Ar-H, *J* 6.9Hz) 6.95(br s, 2H, NH_2) 7.19-7.88 (m, 8H, Ar-H), 7.91 (d, 2H, Ar-H, *J* 6.9 Hz), 9.88 (s, 1H, NH), ^{13}C NMR (75 MHz, DMSO-d6):*δ*, ppm: 36.2, 55.1, 58.1, 67.2, 104.1 ,113.0, 113.7, 114.6, 116.5, 119.3, 120.5, 121.4, 122.4, 124.6, 128.8, 131.4, 132.8, 136.1, 152.1, 153.1, 155.5, 156.9, 157.9, 159.5, 166.0 ; MS (EI): m/z (%) = 495 (M^+). Anal. Calcd. for $C_{28}H_{21}N_3O_6$ (495.49): C, 67.87; H, 4.27; N, 8.48; Found: C, 67.63; H, 4.48; N, 8.65.

2-(4-(2-Amino-3-cyano-5-oxo-4*H*,5*H*-pyrano[3,2-c]chromen-4-yl)phenoxy)-*N*-(4-chlorophenyl)acetamide (14d). Was obtained as a white solid (ethanol-dioxane (1:1)), mp 254-256^{o}C; (method A, 379 mg, 76%; method B, 389 mg, 78%), IR (KBr): ν max: 3465, 3275 (NH_2 and NH), 2198 (CN), 1712 and 1666 (2 C=O) cm^{-1} , ^{1}H NMR (300 MHz, DMSO-d6): *δ*, ppm: 4.41 (s, 1H, pyrane- H4), 4.67 (s, 2H, -OCH_2CO-), 6.95 (br s, 2H, NH_2) 7.22 (d, 2H, Ar-H, *J* 8.7Hz), 7.34-7.88 (m, 8H, Ar-H), 7.91 (d, 2H, Ar-H, *J* 8.7Hz), 10.18 (S, 1H, NH), ^{13}C NMR (75 MHz, DMSO-d6): *δ*, ppm: 36.0, 58.1, 66.8, 103.9, 112.7, 114.5, 116.4, 119.3, 121.4, 122.5, 124.7, 127.5, 128.6, 128.7, 132.9, 136.1, 136.9, 151.9, 153.2, 156.7, 157.9, 159.7, 166.8; MS (EI): m/z (%) = 499 (M^+). Anal. Calcd. for $C_{27}H_{18}ClN_3O_5$ (499.91): C, 64.87; H, 3.63; N, 8.41; Found: C, 64.63; H, 3.49; N, 8.27.

2-(4-((1,3-Dioxo-1,3-dihydro-2*H*-inden-2-ylidene)methyl)phenoxy)-*N*-(*p*-tolyl)acetamide (23a). Was obtained as a white solid (ethanol-dioxane (1:1)), (method A, 302 mg, 76%; method B, 314 mg 79%), mp 244–246^{o}C; IR (KBr): ν max: 3317 (NH), 1725,1641 and 1610 (3CO) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d6): *δ*, ppm: 2.5 (s, 3H, CH_3), 4.89 (s, 2H, -OCH_2-), 7.20 (d, 2H, Ar-H, *J* 9 Hz), 7.40 (d, 2H, Ar-H, *J* 9 Hz), 7.58 (d, 2H, Ar-H, *J* 9 Hz), 7.62 (s, 1H, vinyl-H), 7.91-7.98 (m, 4H, Ar-H), 8.62 (d, 2H, Ar-H, *J* 9 Hz), 10.29 (s, 1H, NH); MS (EI): m/z (%) = 397 (M^+). Anal. Calcd. for $C_{25}H_{19}NO_4$ (397.43): C, 75.55; H, 4.82; N, 3.52. Found: C, 75.25; H, 4.78; N, 3.42.

2-(4-((1,3-Dioxo-1,3-dihydro-2*H*-inden-2-ylidene)methyl)phenoxy)-*N*-(4-methoxyphenyl)acetamide (23b). Was obtained as a white solid (ethanol-dioxane (1:1)), (method A, 297 mg, 72%; method B, 310 mg, 75%), mp 256–258^{o}C; IR (KBr): ν max: 3317 (NH), 1720,1663 and 1582 (3CO) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d6): *δ*, ppm: 3.74 (s, 3H, OCH_3), 4.84 (s, 2H, -OCH_2-), 6.95 (d, 2H, Ar-H, *J* 9 Hz), 7.20 (d, 2H, Ar-H, *J* 9 Hz), 7.55 (d, 2H, Ar-H, *J* 9 Hz), 7.82 (s, 1H, vinyl-H), 7.91-7.96 (m, 4H, Ar-H), 8.89 (d, 2H, Ar-H, *J* 9 Hz), 10.01 (s, 1H, NH) ; MS (EI):

m/z (%) = 413 (M^+). Anal. Calcd. for $C_{25}H_{19}NO_5$ (413.43): C, 72.63; H, 4.63; N, 3.39. Found: C, 72.83; H, 4.53; N, 3.49.

General procedure of synthesis of compound 15a-d

To a mixture of 2-(4-formylphenoxy)-*N*-(aryl)acetamides **7a-d** (1 mmol) and malononitrile **8** (1 mmol) in ethanol (20 mL), piperidine (0.2 mL) was added. The mixture was heated under reflux for 3 h. The crude solid was isolated and recrystallized from the proper solvent.

2-(4-(2,2-Dicyanovinyl)phenoxy)-*N*-phenylacetamide (15a). Was obtained as white solid (ethanol-dioxane (1:1)), (248 mg, 82%), mp 216-218°C; IR (KBr): ν max: 3371 (NH), 2222 (CN), 1674 (CO) cm^{-1}; ^1H NMR (300 MHz, DMSO-d6): *δ*, ppm: 4.87 (s, 2H, -OCH_2-), 7.08-7.34 (m, 5H, Ar-H), 7.59 (d, 2H, Ar-H, *J* 8.1 Hz), 7.97 (d, 2H, Ar-H, *J* 8.1 Hz), 8.40 (s, 1H, vinyl-H), 10.15 (s, 1H, NH); MS (EI): m/z (%) = 303 (M^+). Anal. Calcd. for $C_{18}H_{13}N_3O_2$ (303.32): C, 71.28; H, 4.32; N, 13.85. Found: C, 71.43; H, 4.51; N, 13.77.

2-(4-(2,2-Dicyanovinyl)phenoxy)-*N*-(*p*-tolyl)acetamide (15b). Was obtained as white solid (ethanol-dioxane (1:1)), (266 mg, 84%) mp 194-196°C; IR (KBr): ν max: 3250 (NH), 2122 (CN), 1680 (CO) cm^{-1}; ^1H NMR (300 MHz, DMSO-d6): *δ*, ppm: 2.14 (s, 3H, CH_3), 4.82 (s, 2H, -OCH_2-), 6.96 (d, 2H, Ar-H, *J* 8.4 Hz), 7.13 (d, 2H, Ar-H, *J* 9 Hz), 7.48 (d, 2H, Ar-H, *J* 8.4 Hz), 7.97 (d, 2H, Ar-H, *J* 9 Hz), 8.40 (s, 1H, vinyl-H), 10.05 (s, 1H, NH); Anal. Calcd. for $C_{19}H_{15}N_3O_2$ (317.35): C, 71.91; H, 4.76; N, 13.24. Found: C, 72.11; H, 4.92; N, 13.44.

2-(4-(2,2-Dicyanovinyl)phenoxy)-*N*-(4-methoxyphenyl)acetamide (15c). Was obtained as white solid (ethanol-dioxane (1:1)), (256 mg, 77%) mp > 300°C; IR (KBr): ν max: 3380 (NH), 2190 (CN), 1660 (CO) cm^{-1}; ^1H NMR (500 MHz, DMSO-d6): *δ*, ppm: 3.75 (s, 3H, OCH_3), 4.81 (s, 2H, -OCH_2-), 6.86 (d, 2H, Ar-H, *J* 8.55 Hz), 7.21 (d, 2H, Ar-H, *J* 8.55 Hz), 7.50 (d, 2H, Ar-H, *J* 8.55 Hz), 7.96 (d, 2H, Ar-H, *J* 8.55 Hz), 8.38 (s, 1H, vinyl-H), 10.05 (s, 1H, NH); Anal. Calcd. for $C_{19}H_{15}N_3O_3$ (333.35): C, 68.46; H, 4.54; N, 12.61. Found: C, 68.62; H, 4.71; N, 12.68.

***N*-(4-Chlorophenyl)-2-(4-(2,2-dicyanovinyl)phenoxy)acetamide (15d).** Was obtained as white solid (ethanol-dioxane (1:1)), (286 mg, 85%) mp 230-232°C; IR (KBr): ν max: 3385 (NH), 2222 (CN), 1687 (CO) cm^{-1}; ^1H NMR (500 MHz, DMSO-d6): *δ*, ppm: 4.85 (s, 2H, -OCH_2-), 7.20 (d, 2H, Ar-H, *J* 8.6 Hz), 7.35 (d, 2H, Ar-H, *J* 8.55 Hz), 7.62 (d, 2H, Ar-H, *J* 8.6 Hz), 7.94 (d, 2H, Ar-H, *J* 8.6 Hz), 8.37 (s, 1H, vinyl-H), 10.31 (s, 1H, NH); Anal. Calcd. for $C_{18}H_{12}ClN_3O_2$ (337.76): C, 64.01; H, 3.58; N, 12.44. Found: C, 64.15; H, 3.67; N, 12.60.

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Supplementary Material

^1H and ^{13}C NMR spectra for the prepared compounds can be found *via* the Supplementary Material pdf associated with this article's webpage.

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