Facile one-pot, three-component synthesis of novel fused 4H-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-4H-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 3H-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 4H-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, 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 \(\alpha,\beta\)-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 (Figure 1) have sparked a lot of attention.\(^{17}\)–\(^{19}\) These compounds have been shown to exhibit antibacterial, antiparasitic, anticancer, and antiviral properties.\(^{20}\)–\(^{26}\)

![Figure 1. Structure of 2-phenoxy-N-phenylacetamides.](image)

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, antidiyslipidemic, 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 (Figure 2).

![Figure 2. Structures of 4H-chromenes 2, dihydropyrano[2,3-c]pyrazoles 3, and pyrano[3,2-c]coumarins 4.](image)

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-4H-chromene, 2-amino-3-cyanopyrano[3,2-c]chromene, and 6-
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).

![Chemical structure of 7a-d](image)

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

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-4H-chromen-4-yl)phenoxy)-N-phenylacetamide 10a (Scheme 2).
Scheme 2. Synthesis of (4H-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 \(^1\)H 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-4H-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 dimeredone 9 in ethanol at reflux (Figure 3).

Figure 3. Structures of (4H-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).
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 \(^1\)H NMR spectrum of 12c indicated the presence of two singlet signals at 1.79, and 3.72 ppm 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\(_2\))\(_2\)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-2H-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).

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 \(^1\)H 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 aryldiene-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$_3$O$_2$ 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-((1,3-dioxo-1,3-dihydro-2H-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 \(\delta\) 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 = 118-120°C; IR (KBr) ν 3265 (NH), 1680 (C=O), 1658 (C=O) cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆) δ 4.85 (s, 2H, CH₂), 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 (El, 70 eV): m/z (%) 255 [M⁺]. Anal. Calcd for C₁₅H₁₃NO₃: 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 = 160-162°C; IR (KBr) ν 3278 (NH), 1679 (C=O), 1608 (C=O) cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆) δ 4.85 (s, 2H, CH₂), 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 (El, 70 eV): m/z (%) 289 [M⁺]. Anal. Calcd for C₁₅H₁₂ClNO₃: 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 = 128-130°C; IR (KBr) ν 3271 (NH), 1674 (C=O), 1604 (C=O) cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆) δ 2.25 (s, 3H, CH₃), 4.82 (s, 2H, CH₂), 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 8.7 Hz), 9.88 (s, 1H, NH), 10.05 (s, 1H, CHO) ppm. MS (El, 70 eV): m/z (%) 269 [M⁺]. Anal. Calcd for C₁₅H₁₄NO₂: 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 = 138-140°C; IR (KBr) ν 3268 (NH), 1669 (C=O), 1600 (C=O) cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆) δ 3.72 (s, 3H, O-CH₃), 4.81 (s, 2H, CH₂), 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 (El, 70 eV): m/z (%) 285 [M⁺]. Anal. Calcd for C₁₅H₁₅NO₃: 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-2H-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-2H-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-cyanoo-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromen-4-yl)phenoxy)-N-phenylacetamide (10a). A colorless solid (ethanol-dioxane (1:1)), (method A, 328 mg, 74%; method B, 319 mg, 72%), mp 218–220°C; IR (KBr): v max: 3410, 3317 (NH₂ and NH), 2216 (CN) and 1705,1651 (CO) cm⁻¹; ¹H NMR (300 MHz, DMSO- d₆): δ ppm: 0.95 (s, 3H, CH₃), 1.03 (s, 3H, CH₃), 2.12 (dd, 2H, H₈), 2.49 (s, 2H, H₆), 4.13 (s, 1H, pyrane-H₄), 4.65 (s, 2H, -OCH₂CO- ), 6.89-7.65 (m, 11H, Ar-H+NH₂), 10.02 (s, 1H, NH), ¹³C 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 (El): m/z (%) = 443 (M⁺). Anal. Calcd. for C₂₆H₂₅N₅O₄ (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-cyanoo-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromen-4-yl)phenoxy)-N-(p-tolyl)acetamide (10b). A colorless solid (ethanol-dioxane (1:1)), mp 226–228°C, (method A, 329 mg, 72%; method B, 356 mg, 78%); IR (KBr): v max : 3447,3336 (NH₃), 2189 (CN), 1689 and 1651 (CO) cm⁻¹; ¹H NMR (300 MHz, DMSO- d₆): δ ppm: : 0.94 (s, 3H, CH₃), 1.03 (s, 3H, CH₃), 2.12 (dd, 2H, H₈), 2.25 (s, 3H, CH₃), 2.49 (s, 2H, H₆), 4.13 (s, 1H, pyrane-H₄), 4.62 (s, 2H, -OCH₂CO- ), 6.89-7.52 (m, 10H, Ar-H+NH₂), 9.9 (s, 1H, NH); MS (El): m/z (%) = 457 (M⁺). Anal. Calcd. for C₂₇H₂₇N₅O₄ (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-4H-chromen-4-yl)phenoxy)-N-(4-methoxyphenyl)acetamide (10c). A colorless solid (ethanol-dioxane (1:1)), mp 174–176°C; (method A, 359 mg, 76%; method B, 331 mg, 70%); IR (KBr): v max: 3403, 3366 (NH), 2181 (CN), 1689 and 1651 (CO) cm⁻¹; ¹H NMR (300 MHz, DMSO- d₆): δ, ppm: 0.95 (s, 3H, CH₃), 1.03 (s, 3H, CH₃), 2.12 (dd, 2H, H₈), 2.49 (s, 2H, H₆), 6.79 (d, 2H, Ar-H), 6.87-7.54 (m, 10H, Ar-H+NH₂), 9.8 (s, 1H, NH); MS (EI): m/z (%) = 473 (M⁺). Anal. Calcd. for C₂₇H₂₇N₃O₅ (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-4H-chromen-4-yl)phenoxy)-N-(4-chlorophenyl)acetamide (10d). A colorless solid (ethanol-dioxane (1:1)), mp 246–248°C; (method A, 362 mg, 76%; method B, 377 mg, 79%); IR (KBr): v max: 3402, 3356 (NH), 2183 (CN), 1689 and 1651 (CO) cm⁻¹; ¹H NMR (300 MHz, DMSO- d₆): δ, ppm: 0.94 (s, 3H, CH₃), 1.03 (s, 3H, CH₃), 2.12 (dd, 2H, H₈), 2.49 (s, 2H, H₆), 4.13 (s, 1H, pyrane-H₄), 4.65 (s, 2H, -OCH₂CO-), 6.89-7.65 (m, 10H, Ar-H+NH₂), 10.16 (s, 1H, NH); MS (EI): m/z (%) = 477 (M⁺). Anal. Calcd. for C₂₆H₂₄ClN₃O₄ (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-dihydropyra[2,3-c]pyrazol-4-yl)phenoxy)-N-phenylacetamide (12a). A colorless solid (ethanol-dioxane (1:1)), mp 242-244°C; (method A, 328 mg, 72%; method B, 309 mg, 77%); IR (KBr): v max: 3477, 3333 (NH₂ and 2NH), 2221 (CN), 1691 and 1623 (CO) cm⁻¹; ¹H NMR (300 MHz, DMSO- d₆): δ, ppm: 1.78 (s, 3H, CH₃), 4.55 (s, 1H, pyrane-H₄), 4.66 (s, 2H, CH₂), 6.79 (br s, 2H, NH₂), 6.965 (d, 2H, Ar-H, J8.1 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 C₂₂H₁₉N₅O₃ (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-dihydropyra[2,3-c]pyrazol-4-yl)phenoxy)-N-(p-tolyl)acetamide (12b). A colorless solid (ethanol-dioxane (1:1)), mp 240-242°C; (method A, 324 mg, 78%; method B, 303 mg, 73%); IR (KBr): v max: 3487, 3394 (NH₂ and 2NH), 2196 (CN), 1681 and 1642 (2 C=O) cm⁻¹; ¹H NMR (300 MHz, DMSO- d₆): δ, ppm: 1.78 (s, 3H, CH₃), 2.25 (s, 3H, CH₃), 4.54 (s, 1H, pyrane-H₄), 4.63 (s, 2H, CH₂), 6.78 (br s, 2H, NH₂), 6.96 (d, 2H, Ar-H, J8.4 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 C₂₃H₂₁N₅O₃ (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-dihydropyra[2,3-c]pyrazol-4-yl)phenoxy)-N-(4-methoxyphenyl)acetamide (12c). A colorless solid (ethanol-dioxane (1:1)), mp 240-242°C; (method A, 332 mg, 77%; method B, 315 mg, 73%); IR (KBr): v max : 3479, 3248 (NH₂ and 2NH), 2188 (CN), 1667 and 1647 (2 CO) cm⁻¹; ¹H NMR (300 MHz, DMSO- d₆): δ, ppm: 1.79 (s, 3H, CH₃), 3.72 (s, 3H, -OCH₃), 4.55 (s, 1H, pyrane-H₄), 4.62 (s, 2H, CH₂), 6.79 (br s, 2H, NH₂), 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), 13C 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 C₂₃H₂₁N₅O₃ (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-dihydropyra[2,3-c]pyrazol-4-yl)phenoxy)-N-(4-chlorophenyl)acetamide (12d). A colorless solid (ethanol-dioxane (1:1)), mp 232-234°C; (method A, 339 mg, 78%; method B, 344 mg, 79%); IR (KBr): v max : 3466, 3238 (NH₂ and 2NH), 2223 (CN), 1654 and 1643 (CO) cm⁻¹; ¹H NMR (300 MHz, DMSO- d₆): δ, ppm: 1.78 (s, 3H, CH₃), 4.55 (s, 1H, pyrane-H₄), 4.66 (s, 2H, CH₂), 6.79 (br s, 2H, NH₂), 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), 13C NMR (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 C₂₂H₁₈ClN₃O₅ (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-4H,5H-pyrano[3,2-c]chromen-4-yl)phenoxy)-N-phenylacetamide (14a). A colorless solid (ethanol-dioxane (1:1)), mp 264-266°C; methodology A, 344 mg, 74%; method B, 363 mg, 78%; IR (KBr): v max: 3466, 3244 (NH₂ and NH), 2187 (CN), 1712 and 1672 (CO) cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆): δ, ppm: 4.41 (s, 1H, pyrane H4), 4.67 (s, 2H, -OCH₂CO-), 6.96 (br s, 2H, NH₂) 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 C₂₂H₂₁N₃O₅ (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-4H,5H-pyrano[3,2-c]chromen-4-yl)phenoxy)-N-(p-tolyl)acetamide (14b). A colorless solid (ethanol-dioxane (1:1)), mp 244-246°C; methodology A, 335 mg, 70%; method B, 354 mg, 74%, IR (KBr): v max: 3435, 3297 (NH₂ and NH), 2225 (CN), 1712 and 1658 (CO) cm⁻¹, ¹H NMR (300 MHz, DMSO-d₆): δ, ppm: 2.24 (s, 3H, CH₃), 4.41 (s, 1H, pyrane H4), 4.63 (s, 2H, -OCH₂CO-), 6.95 (br s, 2H, NH₂), 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 C₂₈H₂₁N₃O₅ (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-4H,5H-pyrano[3,2-c]chromen-4-yl)phenoxy)-N-(4-methoxyphenyl)acetamide (14c). A colorless solid (ethanol-dioxane (1:1)), mp 240-242°C; methodology A, 386 mg, 78%; method B, 381 mg, 77%, IR (KBr): v max: 3448, 3274 (NH₂ and NH), 2198 (CN), 1730 and 1654 (CO) cm⁻¹, ¹H NMR (300 MHz, DMSO-d₆): δ, ppm: 3.71 (s, 3H, -OCH₃), 4.41 (s, 1H, pyrane-H4), 4.62 (s, 2H, -OCH₂CO-), 6.88 (d, 2H, Ar-H, J 6.9Hz) 6.95 (br s, 2H, NH₂) 7.19-7.88 (m, 8H, Ar-H), 7.91 (d, 2H, Ar-H, J 6.9 Hz), 9.88 (s, 1H, NH), ¹³C NMR (75 MHz, DMSO-d₆): δ, ppm: 36.2, 55.1, 58.1, 67.2, 104.1,113.0, 113.7, 114.6, 115.6, 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 C₂₈H₂₁N₃O₅ (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-4H,5H-pyrano[3,2-c]chromen-4-yl)phenoxy)-N-(4-chlorophenyl)acetamide (14d). A colorless solid (ethanol-dioxane (1:1)), mp 254-256°C; methodology A, 379 mg, 76%; method B, 389 mg, 78%, IR (KBr): v max: 3465, 3275 (NH₂ and NH), 2198 (CN), 1712 and 1666 (2 C=O) cm⁻¹, ¹H NMR (300 MHz, DMSO-d₆): δ, ppm: 4.41 (s, 1H, pyrane-H4), 4.67 (s, 2H, -OCH₂CO-), 6.95 (br s, 2H, NH₂) 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), ¹³C 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, 152.3, 156.7, 157.9, 159.7, 166.8; MS (EI): m/z (%) = 499 (M⁺). Anal. Calcd. for C₂₈H₂₁ClN₃O₅ (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-2H-inden-2-ylidene)methyl)phenoxy)-N-(p-tolyl)acetamide (23a). A colorless solid (ethanol-dioxane (1:1)), (method A, 302 mg, 76%; method B, 314 mg 79%), mp 244-246°C; IR (KBr): v max: 3317 (NH), 1725,1641 and 1610 (CO) cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆): δ, ppm: 2.5 (s, 3H, CH₃), 4.89 (s, 2H, -OCH₂-), 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 C₂₅H₁₉NO₄ (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-2H-inden-2-ylidene)methyl)phenoxy)-N-(4-methoxyphenyl)acetamide (23b). A colorless solid (ethanol-dioxane (1:1)), (method A, 297 mg, 72%; method B, 310 mg, 75%), mp 256–258°C; IR (KBr): v max: 3317 (NH), 1720,1663 and 1582 (CO) cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆): δ, ppm: 3.74 (s, 3H, OCH₃), 4.84 (s, 2H, -OCH₂-), 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 C₂₅H₁₉NO₅ (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). A colorless solid (ethanol-dioxane (1:1)), (248 mg, 82%), mp 216-218°C; IR (KBr): v max: 3371 (NH), 2222 (CN), 1674 (CO) cm⁻¹; ¹H NMR (300 MHz, DMSO- d₆): δ ppm: 4.87 (s, 2H, -OCH₂-), 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 C₁₈H₁₃N₃O₂ (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). A colorless solid (ethanol-dioxane (1:1)), (266 mg, 84%) mp 194-196°C; IR (KBr): v max: 3250 (NH), 2122 (CN), 1680 (CO) cm⁻¹; ¹H NMR (300 MHz, DMSO- d₆): δ ppm: 2.14 (s, 3H, CH₃), 4.82 (s, 2H, -OCH₂-), 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 C₁₉H₁₅N₃O₂ (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). A colorless solid (ethanol-dioxane (1:1)), (256 mg, 77%) mp > 300°C; IR (KBr): v max: 3380 (NH), 2219 (CN), 1660 (CO) cm⁻¹; ¹H NMR (500 MHz, DMSO- d₆): δ ppm: 3.75 (s, 3H, OCH₃), 4.81 (s, 2H, -OCH₂-), 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 C₁₉H₁₅N₃O₃ (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). A colorless solid (ethanol-dioxane (1:1)), (286 mg, 85%) mp 230-232°C; IR (KBr): v max: 3385 (NH), 2222 (CN), 1687 (CO) cm⁻¹; ¹H NMR (500 MHz, DMSO-d₆): δ ppm: 4.85 (s, 2H, -OCH₂-), 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 C₁₈H₁₂ClN₃O₂ (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 ¹³C NMR spectra for the prepared compounds can be found via the Supplementary Material pdf associated with this article’s webpage.

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