Simple method for synthesis of isolated heterocyclic compounds incorporating 2-(2-bromoacetyl)isoindoline-1,3-dione and 2-(2-cyanoacetyl)isoindoline-1,3-dione

Islam Helmy El Azab a,b & Eman Abd El Rady a

a Chemistry Department, Faculty of Science, South Valley University, Aswan 81528, Egypt
b Chemistry Department, Faculty of Science, Taif University, Al-Haweiah, P.O. box 888, Zip code 21974, Taif, Saudi Arabia

E-mail: ihelmy2003@yahoo.com

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2-(2-Bromoacetyl)isoindoline-1,3-dione 2 and 2-(2-cyanoacetyl)isoindoline-1,3-dione 3 have been used as starting intermediates for synthesis of functionalized heterocyclic derivatives such as, 2-(2-aminothiazol-5-yl)isoindoline-1,3-dione 4, 2-(2-(benzylideneamino)thiazol-5-yl)isoindoline-1,3-dione 5, 2-(2-(3-chloro-2-oxo-4-phenylazetidin-1-yl)thiazol-5-yl)isoindoline-1,3-dione 6, 2-(2-(4-oxo-4,5-dihydrothiazol-2-yl)-1H-pyrazole-4-carbonitrile 10a, 4-(1,3-dioxoisindolin-2-yl)-6-oxo-1-phenyl-1,6-dihydropyridazine-3,5-dicarbonitrile 10b, 1-acetyl-3-(1,3-dioxoisindolin-2-yl)-5-aryl-4,5-dihydro-1H-pyrazole-4-carbonitrile 12, 4-cyano-3-(1,3-dioxoisindolin-2-yl)-5-aryl-4,5-dihydro-1H-pyrazole-1-carbothioamide 13, 3-(1,3-dioxoisindolin-2-yl)-1-(4-oxo-4,5-dihydrothiazol-2-yl)-5-phenyl-4,5-dihydro-1H-pyrazole-4-carbonitrile 14, 3-(1,3-dioxoisindolin-2-yl)-1-(5-(1,3-dioxoisindolin-2-yl)thiazol-2-yl)-5-phenyl-4,5-dihydro-1H-pyrazole-4-carbonitrile 15, 2-(3-amino-5-phenylamino)-1H-pyrazole-4-carboxylatoisoindoline-1,3-dione 17, 2-(5,7-dimethyl-2-(phenylamino)pyrazol)[1,5-a]pyrimidine-3-carbonylisoindoline-1,3-dione 18 and 2-(7-phenyl-2-(phenylamino)pyrazol)[1,5-a]pyrimidine-3-carbonylisoindoline-1,3-dione 20. The synthesized compounds have been characterized by IR, MS, 1H NMR and 13C NMR spectral analysis.

Keywords: 2-Acetylisoindoline-1,3-dione, 3-(1,3-dioxoisindolin-2-yl)-3-oxopropanenitrile, 2-(2-bromoacetyl)isoindoline-1,3-dione, β-lactam, thiazolidin-4-ones

Phthalimide and N-substituted phthalimides are an interesting class of compounds because they possess important biological activities. A series of N-substituted phthalimides presented hypolipidemic activity, and proved to be the most active and reduced plasma cholesterol and triglyceride levels in Swiss white mice significantly. N-Aminoacetylenic phthalimides derivatives were used as anti-inflammatory agents. Also, the antibacterial and antifungal activities of phthalimidopyridines were evaluated. On the other hand, phthalimide and its derivatives are widely employed as feed stock for manufacturing a number of industrial chemicals, primarily pesticides, polymer backbones, as well as plasticisers. Similarly, tetrahydrophthalimide is used as an intermediate for chemical synthesis and includes the productions of pesticides, polymers, and blood pressure lowering, spasmylytic, antitussive and tranquilizer properties. previous studies reported the discovery of the potent non-nucleoside reverse transcriptase inhibitor (NNRTI) classes of o-(2-phthalimidoethyl)-N-arylthiocarbamates. The halogenated cyclicimidides related to N-substituted phthalimide moiety were subjected to hypoglycaemic and anti-hyperlipidemic evaluation. Some of the tested compounds proved to be more potent than the reference drugs glibenclamide and clofibrate. Finally, the cyclicimidides could be considered as useful templates for future development to obtain more potent hypoglycaemic and anti-hyperlipidemic agents.

In view of the aforesaid versatile biological activities and the benefits of N-phthalimide derivatives and as a continuation of the efforts to synthesis isolated and fused heterocyclic compounds, herein is reported a facile and convenient route to 2-(2-bromoacetyl)-isoindoline-1,3-dione 2 and 2-(2-cyanoacetyl)isoindoline-1,3-dione 3 which can be considered as a key intermediate for the synthesis of new N-phthalimides derivatives.

Results and Discussion

The starting material 2-(2-bromoacetyl)isoindoline-1,3-dione 2, used in this study was prepared in
quantitative yield using a modified procedure by heating N-acetylphthalimide in dioxane with N-bromo-succinimide as brominating agent. Treatment of 2-(2-bromoacetyl) isoidoline-1,3-dione 2 with potassium cyanide gave 2-(2-cyanoacetyl)isoindoline-1,3-dione 3 in high yield, and also considered as a good precursor for synthesis of isolated heterocyclic compounds (Scheme I).

Compound 2 reacted with thiourea in refluxing ethanolic piperidine solution affording the corresponding 2-(2-aminothiazol-5-yl)isoindoline-1,3-dione 4. The structure of 4 has been assigned as a reaction product on the basis of analytical and spectral data. The IR spectrum displayed absorption bands at 1690-1715 (C=O amide), 3360 cm⁻¹ due to NH₂ function. The ¹H NMR spectrum (DMSO-d₆) exhibited two singlet signals at δ 6.57 and 6.22 specific for thiazole-H-4 proton and amino protons, respectively, a multiplet signal at δ 7.20-7.95 region owing to aromatic protons. The mass spectrum showed a molecular ion peak at m/z = 245, corresponding to a molecular formula C₁₁H₉N₂O₂S. Compound 4 condensed easily with benzaldehyde in ethanol containing piperidine at reflux temperature affording the corresponding Schiff base 5. The IR spectrum of 5 showed the absence of the absorption of the amino group. The ¹H NMR spectrum of 5 showed two singlet signals at δ 6.21 and 6.75 due to the N=CH group and thiazole-H4 respectively, and a multiplet at δ 6.93–7.85 for aromatic protons. The MS of 5 showed a fragment at m/z 333 (M, 60%). A β-lactam derivative 6 is formed by the addition of chloroacetyl chloride to the Schiff base 5 via elimination of two hydrogen chloride molecules. The IR spectrum of 6 showed the presence of absorption bands at 1795-1705 cm⁻¹ due to (2CO amide) function. The ¹H NMR spectrum of 6 showed two doublet signals at δ 3.95 and 4.49 for the protons at C3 and C4 of the azetidinone. The MS of 6 displayed an intense ion peak at m/z 410 (M, 50%). A similar reactivity of Schiff base 5 is shown by the thioglycolic acid; formation of the isolated 2-(2-(2,5-dioxothiazolidin-3-yl)thiazol-5-yl)isoindoline-1,3-dione 7 takes place by the nucleophilic addition of thiol function on the imino carbon of Schiff base, which subsequently cyclized via loss of water affording 7. The MS of 7 showed a peak at m/z 407([M⁺, 55%) (Scheme II).

Direct coupling of 2-(2-bromoacetyl)isoindoline-1,3-dione 2 and/or 2-(2-cyanoacetyl)isoindoline-1,3-dione 3 with substituted benzene diazonium chloride gives the corresponding 2-(1,3-dioxoisoidolin-2-yl)-2-oxo-N'-phenylacetoxydrazonoyl bromide 8a and 2-(1,3-dioxoisoidolin-2-yl)-2-oxo-N'-phenylacetoxydrazonyol cyanide 8b in good yields. Compound 8 contains three active centers which attract to explore its utility to prepare new heterocyclic derivatives. Thus, treatment with ethyl cyanoacetate in boiling ethanol containing few drops of piperidine afforded the corresponding 10 via the intermediate 9 which formed through condensation reaction, which subsequently cyclized through elimination of ethanol as shown in Scheme III. The above assumption was based on the basis of spectral and elemental analysis.

The key chalcone intermediates 11 were synthesized through condensation of equimolar amounts of 2-(2-cyanoacetyl)isoindoline-1,3-dione 3 with some aromatic aldehydes in ethanol containing piperidine at reflux temperature (Scheme IV).

In the present work, two types of pyrazole derivatives were prepared utilizing different reaction conditions. In acidic media, the novel N-acetyl pyrazole derivatives 12 were prepared by heating at reflux the corresponding chalcone 11 with hydrazine hydrate in acetic acid for 4 hr. N-Acetyl pyrazoles were obtained rather than the non-acetylated ones due to heating in glacial acetic acid for long periods of time (Scheme IV). The presence of N-acetyl group was established using IR and ¹H NMR spectra whereas IR showed a strong absorption band at 1692-1710 cm⁻¹ for the three carbonyl groups, ¹H NMR spectra revealed the presence of singlet signal integrating three protons around δ 2.23 due to the methyl group confirming its existence.

![Scheme I](image-url)
On the other side, upon using basic media, the novel 1-thiocarbamoyl pyrazole derivatives 13 were obtained by heating at reflux equimolar amounts of thiosemicarbazide and the corresponding α,β-unsaturated ketones 11 in hot ethanolic NaOH solution for 8 hr (Scheme IV). These 1-thiocarbamoyl pyrazole derivatives were characterized using elemental and spectral analysis. Whereas IR of 13 showed strong absorption bands at 1332, 3480 cm\(^{-1}\) due to C=S and NH\(_2\) group respectively.

Treatment of compound 13 with chloroacetyl chloride in ethanolic triethylamine led to 3-(1,3-dioxo-isoindolin-2-yl)-1-(4-oxo-4,5-dihydrothiazol-2-yl)-5-phenyl-4,5-dihydro-1H-pyrazole-4-carbonitrile 14. The same product was obtained through the reaction of 13 with chloroacetic acid in glacial acetic acid in the presence of catalytic amount of sodium acetate. A third route for the synthesis of 14 involved the interaction of 13 with ethyl bromoacetate in ethanol as shown in Scheme V.

On the other side, reaction of 13 with compound 2 in refluxing ethanol yielded the new bisphthalimide compound 15. The structure of compound 15 was established based on analytical and spectral analysis. The IR spectrum of compound 15 confirmed the presence of intense absorption bands at 1690-1715 and 2202 cm\(^{-1}\) due to four carbonyl and cyano groups, respectively and disappearance of bands due to C=S and NH\(_2\) group respectively. The MS of 15 showed m/z at 543 [M-1]\(^+\), 20%. The \(^1\)H NMR spectrum of 15 showed two doublet signals at δ 5.31 and 5.40 attributed to pyrazole protons and a multiplet at δ 7.23-7.54 attributed to thiazole and aromatic protons, respectively (Scheme VI).

Furthermore, treatment of compound 3 with phenyl isothiocyanate in DMF and in the presence of potassium hydroxide, at RT, followed by treatment with methyl iodide afforded 2-(1,3-dioxoisindoline-2-carbonyl)-3-(methylthio)-3-(phenylamino)acrylonitrile 16 (Scheme VII). The structure of 16 was established
on the basis of its elemental analysis and spectral data. The IR spectrum of 16 showed absorption bands at 1692-1718, 2202 and 3268 cm\(^{-1}\) due to three carbonyl, cyano and NH groups, respectively. The MS of 16 showed m/z at 363 (M\(^+\)), 25\%. The \(^1\)H NMR spectrum of 17 displayed three singlet signals at δ 6.48, 9.12 and 10.12 corresponding to NH\(_2\), PhNH-and-NH-of pyrazole ring protons respectively, and a multiplet at δ 6.75-7.69 attributed to aromatic protons.

3-Amiopyrazoles are versatile reagents and have been extensively used as synthetic intermediates for the synthesis of poly substituted fused pyrazoles of potential biological activity\(^{25,26}\). It was thus of interest to study the reactivity of 3-aminopyrazole derivative 17 towards a variety of chemical reagents. Thus, cyclocondensation reaction of compound 17 with 1,3-dicarbonyl compounds were also studied. The
reaction of 17 with acetylacetone in boiling acetic acid gave a single product, as evidenced by TLC. The reaction product can be formulated as 2-(5,7-dimethyl-2-(phenylamino)pyrazolo[1,5-a]pyrimidine-3-carbonyl)isoindoline-1,3-dione 18, (Scheme VIII), evidence for the assigned structures being provided by analytical and spectroscopic data, the MS of 18 showed m/z at 412 [M+1]+, 40%.

Furthermore, we also investigated the reactivity of aminopyrazole 17 towards enaminone with the aim of preparing pyrazolo[1,5-a]pyrimidine. Thus, reaction of 17 with 3-(dimethylamino)-1-phenylprop-2-en-1-one 27,28 in glacial acetic acid at reflux afforded 2-(7-phenyl-2-(phenylamino)pyrazolo[1,5-a]pyrimidine-3-carbonyl)isoindoline-1,3-dione 20 (Scheme VIII). The structure of compound 20 was established based on analytical and spectral analysis. The IR spectrum of compound 20 confirmed the presence of intense absorption bands at 1691-1707 and 3350 cm⁻¹ due to three carbonyl and NH groups, respectively. The MS of 20 showed m/z at 459 (M⁺), 55%. The ¹H NMR spectrum of 20 showed in addition to the expected signals two doublet signals at δ 8.11 and 8.86 assigned to two vicinal protons of the pyrimidine ring H-5 and H-4, respectively. The formation of compound 20 is assumed to take place via an initial Michael addition of the exocyclic amino group in 17 to the activated double bond in the enaminone followed by cyclization and aromatization via loss of both dimethylamine and water molecules.
Experimental Section

Melting points were determined on a Gallenkamp electro thermal melting point apparatus and are uncorrected. IR spectra were recorded as KBr pellets using a FTIR unit Bruker-vector 22 spectrophotometer. 1H NMR (200 and 500 MHz) and 13C NMR (125 MHz) spectra were recorded on a Bruker AC 200 and Avance 500 MHz spectrometers in DMSO-<sub>d6</sub> or CDCl<sub>3</sub> as a solvent and tetramethylsilane (TMS) as an internal standard. Chemical shifts are reported in δ units (ppm). Mass spectra were recorded on a Hewlett Packard MS-5988 spectrometer at 70 eV. Elemental analysis was carried out at the Micro Analytical Center of Cairo University, Egypt.

Synthesis of 2-(2-bromoacetyl)isoindoline-1,3-dione, 2. To a solution of N-acetyl phthalimide 1 (1 mmol) in dioxane (20 mL), N-bromosuccinimide (1 mmol) was added. The reaction mixture was heated at reflux for 4 hr and cooled to RT. The solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (EtOAc/ hexane 1:4) to give 2 as yellow crystals, m.p. 285-287°C; yield: 0.8 g, 70% (DMF-H<sub>2</sub>O (3:1)). IR (KBr): 1713 cm<sup>-1</sup> (CO); 1H NMR (DMSO-<sub>d6</sub>): δ 3.65 (s, 2H, CH<sub>2</sub>), 7.81-7.89 (m, 4H, Ar-H); 13C NMR (CDCl<sub>3</sub>): δ 24.8 (CH<sub>2</sub>), 123.71, 132.01 (benzene), 169.21 (2CO-amide), 175.3 (CO-acetyl); MS: m/z (%) 268 (M<sup>+</sup>, 45%) and 267 ([M-1]<sup>+</sup>, 24%). Anal. Calcd for C<sub>10</sub>H<sub>6</sub>BrNO<sub>3</sub> (268.06): C, 44.81; H, 2.26; N, 5.23. Found: C, 44.89; H, 2.34; N, 5.44%.

Synthesis of 3-(1,3-dioxoissoindolin-2-yl)-3-oxopropanenitrile, 3. To a solution of 2 (1 mmol) in ethanol (30 mL), was added stepwise potassium cyanide (1 mmol) in water (20 mL). The reaction mixture was stirred for 2 hr at 0°C and then allowed to stir at RT for 24 hr. Then the mixture was poured into acidified cold water and the resulting precipitate was filtered off and washed with 100 mL of cold water to give 3 as yellow crystals. m.p. 198-200°C; yield: 0.7 g, 65% (Dioxane/H<sub>2</sub>O). IR (KBr): 1710 (CO), 2210 cm<sup>-1</sup> (CN); 1H NMR (DMSO-<sub>d6</sub>): δ 4.01 (s, 2H, CH<sub>2</sub>), 7.81-7.89 (m, 4H, Ar-H); 13C NMR (CDCl<sub>3</sub>): δ 22.2 (CH<sub>2</sub>), 123.71, 132.01 (benzene), 169.21 (3CO-amide), 125.7 (CN); MS: m/z (%) 214 (M<sup>+</sup>, 45%). Anal. Calcd for C<sub>11</sub>H<sub>6</sub>N<sub>2</sub>O<sub>3</sub> (214): C, 61.69; H, 2.82; N, 13.08. Found: C, 61.75; H, 2.90; N, 13.13%.

Synthesis of 2-(2-aminothiazol-5-yl)isoindoline-1,3-dione, 4. A mixture of 2 (0.26 g, 1 mmol), thiourea (0.67 g, 1 mmol) in 20 mL of ethanol containing 0.2 mL of piperidine was refluxed for 5 hr. After cooling, the mixture was poured into ice/water mixture. The product that formed was collected by
filtration and washed several times with cold water to give 4 as deep yellow powder. m.p. 158-60°C; yield: 45% (ethanol). IR (KBr): 1690-1715 (two amide CO), 3360 cm⁻¹ (NH₂); ¹H NMR (DMSO-d₆): δ 6.57 (s, 1H, thiazole), 7.20-7.95 (m, 4H, Ar-H), 8.22 (s, 2H, NH₂); MS: m/z (%) 245 (M⁺, 55%). Anal. Calcd for C₁₁H₈N₂O₂S (245): C, 53.75; H, 2.95; N, 17.34%. Found: C, 53.75; H, 2.95; N, 17.34%.

Synthesis of 2-(2-(benzyldeneamino)thiazol-5-yl)isoindoline-1,3-dione, 5. An equimolar mixture of 4 (0.24 g, 1 mmol) and benzaldehyde (0.22 g, 1 mmol) was dissolved in ethanol (30 mL) in the presence of piperidine (0.2 mL) and refluxed for 6 hr. The solid product formed after cooling was collected by filtration and purified by recrystallization from ethanol to yield yellow crystals. Yield: 0.3 g, 80%. m.p. 256-58°C. IR (KBr): 1695-1699 cm⁻¹ (CO); ¹H NMR (DMSO-d₆): δ 6.21 (s, 1H, N=CH), 6.57 (s, 1H, thiazole), 6.93-7.85 (m, 9H, Ar-H); MS: m/z (%) 334 ([M+1]⁺, 60%). Anal. Calcd for C₁₃H₁₁N₂O₃S (334): C, 64.85; H, 3.33; N, 12.60. Found: C, 64.99; H, 3.46; N, 12.74%.

Synthesis of 2-(2-(3-chloro-2-oxo-4-phenylazetidin-1-yl)thiazol-5-yl)isoindoline-1,3-dione, 6. To a well stirred solution of 5 (0.3 g, 1 mmol) and triethylamine (0.14 mL, 1 mmol) in dry benzene (20 mL) was added hydrazonoyl bromide, 8a, and/or hydrazonoyl cyanide, 8b. The precipitate of triethylamine hydrochloride was separated off, washed with ether thoroughly, dried and purified by recrystallization from methanol to yield compounds 7a,b respectively.

General procedure for the synthesis of 2-(1,3-dioxoisindolin-2-yl)-2-oxo-N'-phenylaceto-hydrazonoyl bromide, 8a and its derivative 8b. To a mixture of aniline (1 mmol) in 10 mL of ethanol and 3 mL of concentrated hydrochloric acid (0.76 g, 1 mmol) of sodium nitrate in 15 mL of cold water was added drop wise during a period of 15 min. Then the mixture was added to 10 mL of a well stirred cold ethanol solution of compound 2 and/or 3 (1 mmol) in the presence of 2 g of anhydrous sodium acetate. The reaction mixture was left overnight at RT. The resulting solid product formed was collected by filtration, washed by water and purified by recrystallization from methanol to yield compounds 8a,b respectively.

2-(1, 3-Dioxoisindolin-2-yl)-2-oxo-N'-phenylaceto-hydrazonoyl bromide, 8a: White crystals; m.p. 198-200°C; yield: 55% (methanol). IR (KBr): 1690-1705 (3 CO), 3210 cm⁻¹ (NH); ¹H NMR (DMSO-d₆): δ 7.38-7.89 (m, 10H, Ar-H + NH); MS: m/z (%) 372 (M⁺, 40%). Anal. Calcd for C₁₉H₁₈BrN₂O₄ (372): C, 51.63; H, 2.71; N, 11.29. Found: C, 51.77; H, 2.86; N, 11.34%.

2-(1, 3-Dioxoisindolin-2-yl)-2-oxo-N'-phenylaceto-hydrazonoyl cyanide, 8b. Brown crystals; m.p. 217-19°C; yield: 70% (methanol). IR (KBr): 1693-1710 (3 CO), 2210 (CN), 3210 cm⁻¹ (NH); ¹H NMR (ppm, DMSO-d₆): δ 7.34-7.87 (m, 10H, Ar-H & NH); MS: m/z (%) 318 (M⁺, 60%). Anal. Calcd for C₁₉H₁₈BrN₂O₃S (318): C, 64.15; H, 3.17; N, 17.60. Found: C, 64.33; H, 3.23; N, 17.71%.

General procedure for the synthesis of 6-bromo-5-(1,3-dioxoisindolin-2-yl)-3-oxo-2-phenyl-2,3-dihydro-pyrudazine-4-carboni-trile, 10a and its derivative 10b. A mixture of 8a (0.37 g, 1 mmol), ethylcyanoacetate (0.13 mL, 1 mmol) in 20 mL of ethanol containing 0.1 mL of piperidine as catalyst was refluxed for 3 hr. The compound formed during reflux was collected by filtration and purified by recrystallization from Dioxane/H₂O to form compound 10a.
Analogously, compound 8b reacted with ethylcyanoacetate (1 mmol) to afford compound 10b.

6-Bromo-5-(1,3-dioxoindolin-2-yl)-3-oxo-2-phenyl-2,3-dihydropyridazine-4-carbonitrile, 10a. Yellow crystals; m.p. 236-38°C; yield: 60% (Dioxane/H2O). IR (KBr): 1692-1704 cm\(^{-1}\) (CO); \(^1\)H NMR (DMSO-d\(_6\)): \(\delta 7.38-7.89\) (m, 9H, Ar-H); MS: m/z (%) 420 (M\(^+\), 40%). Anal. Calcd for C\(_{25}\)H\(_{18}\)BrN\(_3\)O\(_4\) (420): C, 54.18; H, 2.15; N, 13.30. Found: C, 54.26; H, 2.33; N, 13.41%.

4-(1,3-Dioxoindolin-2-yl)-6-oxo-1-phenyl-1,6-dihydropyridazine-3,5-dicarbonitrile, 10b. Yellow crystals; m.p. 168-70°C; yield: 65% (MeOH/H\(_2\)O). IR (KBr): 1693-1709 (CO), 2212 cm\(^{-1}\) (CN); \(^1\)H NMR (DMSO-d\(_6\)): \(\delta 7.34\) (m, 9H, Ar-H); \(^13\)C NMR (CDCl\(_3\)): \(\delta 128.00, 128.90, 140.03\) (Ph); MS: m/z (%) 164.00 (CO-pyridazine), 165.81(2CO-amide), 118.50, 137.53, 138.68, 140.03, 141.55 (Ph). Anal. Calcd for C\(_{21}\)H\(_{15}\)BrN\(_2\)O\(_3\) (347): C, 60.74; H, 2.25; N, 8.80. Found: C, 60.78; H, 2.33; N, 8.97%.

**General procedure for the synthesis of 2-(1,3-dioxoindolin-2-carbonyl)-3-phenylacrylonitrile, 11a and its derivatives 11b-e.** An equimolar mixture of 3 (0.21 g, 1 mmol) and benzaldehyde (0.22 g, 1 mmol) was dissolved in ethanol (30 mL) in the presence of piperidine (0.2 mL) and refluxed for 6 hr. The solid product formed after cooling was collected by filtration and purified by recrystallization from MeOH-H\(_2\)O (3:1) to form 11a, which was purified by recrystallization from methanol. Analogously, compound 3 reacted with different aldehydes (1 mmol) to afford compounds 11b-e.

2-(1,3-Dioxoindolin-2-carbonyl)-3-phenylacrylonitrile, 11a. Pale green crystals; m.p. 180-83°C; yield: 65% (MeOH/H\(_2\)O). IR (KBr): 1690-1717 (CO), 2215 cm\(^{-1}\) (CN); \(^1\)H NMR (DMSO-d\(_6\)): \(\delta 7.02-7.89\) (m, 9H, Ar-H); MS: m/z (%) 337 (M\(^+\), 60%). Anal. Calcd for C\(_{18}\)H\(_{12}\)N\(_3\)O\(_3\) (337): C, 64.20; H, 2.69; Cl, 10.53; N, 8.32. Found: C, 64.32; H, 2.76; Cl, 10.64; N, 8.42%.

**General procedure for the synthesis of 1-acetyl-3-(1,3-dioxoindolin-2-yl)-5-phenyl-4,5-dihydro-2H-pyrazole-4-carbonitrile, 12a and its derivatives 12b-e.** An equimolar mixture of 11 (1 mmol) and hydrazine hydrate (1 mmol) was dissolved in acetic acid (30 mL) and refluxed for 6 hr. The reaction mixture was concentrated to dryness under reduced pressure. The solid product was separated off, washed with methanol and purified by recrystallization from methanol.

1-Acetyl-3-(1,3-dioxoindolin-2-yl)-5-phenyl-4,5-dihydro-2H-pyrazole-4-carbonitrile, 12a. Yellow crystals; m.p. 178-90°C; yield: 63% (methanol). IR (KBr): 1690-1717 (3 CO), 2215 cm\(^{-1}\) (CN); \(^1\)H NMR (DMSO-d\(_6\)): \(\delta 7.02-7.89\) (m, 9H, Ar-H); MS: m/z (%) 358 (M\(^+\), 75%). Anal. Calcd for C\(_{18}\)H\(_{12}\)N\(_3\)O\(_3\) (358): C, 70.03; H, 3.94; N, 15.63. Found: C, 67.23; H, 3.99; N, 15.77%.

1-Acetyl-3-(1,3-dioxoindolin-2-yl)-5-(4-hydroxyphenyl)-4,5-dihydro-2H-pyrazole-4-carbonitrile, 12b. Pale green; m.p. 269-71°C; yield: 68% (MeOH/H\(_2\)O). IR (KBr): 1692-1710 (3 CO), 2208 cm\(^{-1}\) (CN); \(^1\)H NMR (DMSO-d\(_6\)): \(\delta 7.59\) (m, 8H, Ar-H), 10.12 (s, 1H, OH); MS: m/z (%) 374 (M\(^+\), 55%). Anal. Calcd for C\(_{18}\)H\(_{12}\)N\(_3\)O\(_3\) (374): C, 64.17; H, 3.77; N, 14.97. Found: C, 64.22; H, 3.88; N, 14.90%.

1-Acetyl-3-(1,3-dioxoindolin-2-yl)-5-(4-nitrophenyl)-4,5-dihydro-2H-pyrazole-4-carbonitrile, 12c.
1-Acetyl-(1, 3-dioxoisindolin-2-yl)-5-(2-nitropheryl)-4,5-dihydro-1H-pyrazole-4-carbonitrile, 12d. Colorless crystals; m.p. 209-11°C; yield: 63% (MeOH/H₂O). IR (KBr): 3445 cm⁻¹ (CN); ³H NMR (DMSO-d₆): δ 2.64 (s, 3H, CH₃). Pale yellow powder; m.p. 245-7°C; yield: 48% (ethanol). IR (KBr): 1692-1710 (CO), 2209 cm⁻¹ (CN). Anal. Calcd. for C₁₀H₁₅ClN₂O₃S (420): C, 55.68; H, 2.95; N, 19.99; S (420): C, 54.28; H, 2.88; N, 19.99.

4-Cyano-3-(1, 3-dioxoisindolin-2-yl)-5-(2-nitropheryl)-4,5-dihydro-1H-pyrazole-1-carbothioamide, 13a and its derivatives 13b-e. An equimolar mixture of 11 (1 mmol) and semithiocarbazide (0.091 g, 1 mmol) was dissolved in ethanol (30 mL) in the presence of sodium (0.2 g) and refluxed for 6 hr. The solid product formed during reflux was removed by filtration and the filtrate was poured into acidified ice/water. The precipitate formed was washed with water, dried and purified by recrystallization from methanol/water.

4-Cyano-3-(1, 3-dioxoisindolin-2-yl)-5-phenyl-4,5-dihydro-1H-pyrazole-1-carbothioamide, 13a. Yellow crystals; m.p. 280-82°C; yield: 56% (ethanol). IR (KBr): 1692-1710 (CO), 2209 (CN). Anal. Calcd. for C₁₀H₁₅ClN₂O₃S (409): C, 55.76; H, 2.84; N, 19.87; S (409): C, 55.71; H, 2.89; Cl, 8.45; N, 17.23%.

Synthesis of 3-(1, 3-dioxoisindolin-2-yl)-1-(4-oxo-4,5-dihydrothiazol-2-yl)-5-phenyl-4,5-dihydro-1H-pyrazole-4-carbonitrile, 14. Method A. An equimolar mixture of 13a (0.37 g, 1 mmol) and chloroacetetyl chloride (1 mmol) in 20 mL of ethanol containing 0.1 mL of triethy amine as catalyst was refluxed for 6 hr. The reaction mixture was concentrated to dryness under reduced pressure. The resultant was separated off, washed with methanol and purified by recrystallization from ethanol as yellow crystals, m.p. 265-67°C; yield: 52% (ethanol).
Method B. A mixture of compound 13a (0.74 g, 2 mmol) and chloro acetic acid (2 mmol) was dissolved in glacial acetic acid (20 mL) to which anhydrous sodium acetate (0.5 g) was added. The reaction mixture was heated on water bath for 2 hr, and then poured into ice-cold water. The resulting precipitate was filtered off, dried and purified by recrystallization from ethanol as yellow crystals. Yield: 65% (ethanol).

Method C. To a solution of compound 13a (0.74 g, 2 mmol) in absolute ethanol (30 mL) was added ethyl bromoacetate (0.32 mL, 2 mmol). The reaction mixture was refluxed for 2 hr, and then left to cool, diluted with water and allowed to stand overnight. The precipitate was filtered, washed with methanol and purified by recrystallization from ethanol as yellow crystals. Yield: 58% (ethanol).

IR (KBr): 1692-1704 (CO), 2209 cm⁻¹ (CN); ¹H NMR (DMSO-d₆): δ 3.97 (s, 2H, CH₂ thiazole), 5.37 (d, J = 6.01 Hz, 1H, H-4 pyrazole), 5.43 (d, J = 6.01 Hz, 1H, H-5 pyrazole), 6.87-7.69 (m, 9H, Ar-H); ¹³C NMR (CDCl₃): δ 31.9 (C-4-pyrazole), 36.7 (C-5-thiazole), 38.7 (C-5-pyrazole), 116.9 (CN), 156.0 (C-3-pyrazole), 123.7, 132.0, 132.2 (benzene), 165.8 (2CO-amide), 118.5, 128.0, 128.9, 140.0 (Ph), 200.0 (CO-thiazole). MS: m/z (%): 415 (%), 403 (31%), 381 (27%), 359 (18%), 337 (18%), 325 (44%). Anal. Calcd for C₂₂H₁₁NO₃S (415): C, 60.71; H, 3.32; N, 20.11%. Found: C, 60.85; H, 3.45; N, 19.97%.

Synthesis of 3-[(3-dioinoisoindolin-2-yl)-1-(5-(1,3-dioinoisoindolin-2-yl)thiazol-2-yl)-5-phenyl-4,5-dihydro-1H-pyrazole-4-carbonyl]-4-carbonitrile, 15. An equimolar mixture of 13a (1 mmol) and 2 (1 mmol) in 20 mL of ethanol containing 0.1 mL of piperidine as catalyst was refluxed for 6 hr. The reaction mixture was concentrate to dryness under reduced pressure. The resultant was separated off, washed with methanol and purified by recrystallization from ethanol as brown crystals, m.p. 158-60°C; yield: 80% (ethanol). IR (KBr): 1690-1715 (4 amide CO), 2225 cm⁻¹ (CN); ¹H NMR (DMSO-d₆): δ 5.31 (d, J = 6.01 Hz, 1H, H-4 pyrazole), 5.40 (d, J = 6.01 Hz, 1H, H-5 pyrazole), 7.23-7.54 (m, 14H, Ar-H & thiazole proton); MS: m/z (%) 543 ([M-1]+, 20%). Anal. Calced for C₂₆H₁₁NO₅S (544): C, 63.96; H, 2.96; N, 15.43. Found: C, 63.99; H, 2.12; N, 15.54%.

Synthesis of 3-[(3-dioinoisoindolin-2-carbonyl)-3-(methylthio)-3-(phenylamino)acrylonitrile, 16. To a stirred solution of potassium hydroxide (0.11 g, 2 mmol) in dimethylformamide (20 mL) was added compound 3 (0.428 g, 2 mmol). After stirring for 30 min, phenyl isothiocyanate (0.27 g, 2 mmol) was added to the resulting mixture. Stirring was continued for 6 hr, and then methyl iodide (0.28 g, 2 mmol) was added. Stirring was continued for additional 3 hr. Then, the reaction mixture was poured onto crushed ice. The solid product that formed was filtered off, dried and purified by recrystallization from ethanol to afford 16, as yellow crystals, m.p. 112-14°C; yield: 85% (ethanol). IR (KBr): 1690 (CO), 2225 (CN), 3350 cm⁻¹ (NH); ¹H NMR (DMSO-d₆): δ 2.45 (s, 3H, SCH₃), 6.51-7.89 (m, 11H, Ar-H); ¹³C NMR (CDCl₃): δ 17.6 (Me), 24.6 (Me), 92.0 (C-4-pyrazole), 108.8 (C-5-pyrimidine), 117.5, 122.4, 129.9, 140.9 (Ph), 132.0 (C-5-pyrazole), 146.3 (C-6-pyrimidine), 164.8 (C-4-pyrimidine), 125.8, 133.0, 141.2 (benzene), 193.5, 196.5 (3 CO); MS: m/z (%) 412 ([M+H]+, 40%.

Synthesis of 2-(3-phenylamino)-4,5-dihydro-1H-pyrazole-4-carbonitrile, 17. A mixture of 16 (0.67 g, 2 mmol) and hydrazine hydrate (0.5 mL, 5 mmol) was heated on steam bath for 1 hr and then the reaction mixture was left to cool. The reaction mixture was triturated with ethanol and the solid product was separated off, washed with methanol and purified by recrystallization from ethanol to give compound 17, as colorless crystals; m.p. 248-50°C; yield: 55% (ethanol). IR (KBr): 1686-1702 (3 CO), 2209 (CN), 3355 (NH), 3420 cm⁻¹ (NH₂); ¹H NMR (DMSO-d₆): δ 6.48 (s, 2H, NH₂), 6.83-7.89 (m, 9H, Ar-H), 9.12 (s, 1H, NH-Ph), 10.12 (s, 1H, NH pyrazole ring). ¹³C NMR (CDCl₃): δ 84.5 (C-4-pyrazole), 151.7 (C-3-pyrazole), 153.0 (C-5-pyrazole), 123.7, 132.0, 132.2 (benzene), 118.5, 128.0, 128.9, 140.0 (Ph), 165.8, 168.6 (3CO); MS: m/z (%) 347 (M⁺, 25%). Anal. Calcd for C₁₉H₁₃N₃O₃ (347.33): C, 62.24; H, 3.77; N, 20.16. Found: C, 62.02; H, 3.32; N, 20.11%.

Synthesis of 2-(5,7-dimethyl-2-(phenylamino)pyrazole[1, 5-a]pyrimidine-3-carbonitrile, 18. A mixture of 17 (0.68 g, 2 mmol) and an equimolar amount of acetylace (0.2 mL, 2 mmol) in glacial acetic acid (20 mL) was refluxed for 5 hr. The reaction mixture was poured onto crushed ice, and the separated solid was filtered off, dried well and purified by recrystallization from ethanol to afford 18 as white crystals, m.p. 278-80°C; yield: 70% (ethanol). IR (KBr): 1690-1715 (3 CO), 3350 cm⁻¹ (NH); ¹H NMR (DMSO-d₆): δ 2.50 (s, 3H, CH₃), 2.73 (s, 3H, CH₃), 6.61-7.89 (m, 10H, Ar-H and methine proto of pyrimidine), 10.71 (s, 1H, NH-Ph); ¹³C NMR (CDCl₃): δ 17.6 (Me), 24.6 (Me), 92.0 (C-4-pyrazole), 108.8 (C-5-pyrimidine), 117.5, 122.4, 129.9, 140.9 (Ph), 132.0 (C-5-pyrazole), 146.3 (C-6-pyrimidine), 164.8 (C-4-pyrimidine), 125.8, 133.0, 141.2 (benzene), 193.5, 196.5 (3 CO); MS: m/z (%) 412 ([M+H]+, 40%.

Anal. Calcd for C₁₉H₁₃N₃O₃ (411.13): C, 67.15; H, 4.16; N, 17.02. Found: C, 65.89; H, 4.01; N, 16.99%.
Synthesis of 2-(7-phenyl-2-(phenylamino)-
pyrazolo[1, 5-a]pyrimidine-3-carbonyl)isoindoline-
1,3-dione, 20. A mixture of 17 (0.34 g, 1 mmol) in
glacial acetic acid (20 mL) which was treated with 3-(dimethylamino)-1-phenylprop-2-en-1-one (0.175 g, 
1 mmol) was heated under reflux for 2 hr. The solvent 
was then evaporated in vacuo and the mass triturated 
with ethanol. The solid deposited was collected by 
filtration and purified by recrystallization from ethanol to 
afford 20 as yellow crystals, m.p. 259-61°C; yield: 
55% (ethanol). IR (KBr): 1691-1707 (3 CO), 3350 
\(^{1}\)H NMR (DMSO-\(d_{6}\)): \(\delta \) 6.61-7.89 (m, 14H, 
Ar-H), 8.23 (d, \(J = 10.05 \) Hz, 1H, pyrimidine H-4), 
8.34 (d, \(J = 10.05 \) Hz, 1H, pyrimidine H-5), 10.54 
(s, 1H, NH-Ph); \(^{13}\)C NMR (CDCl\(_3\)): \(\delta \) 92.0 (C-4-
pyrazole), 115.5 (C-5-pyrimidine), 118.5, 128.0, 
128.9, 140.0 (2Ph), 132.0 (C-5-pyrazole), 146.3 (C-6-
pyrimidine), 158.1 (C-4-pyrimidine), 123.7, 132.0, 
132.2 (benzene), 193.5, 196.3 (3 CO); MS: \(m/z \) (%) 459 (M\(^{+}\), 55%). Anal. Calcd for C\(_{27}\)H\(_{23}\)N\(_{6}\)O\(_{3}\) (459.46): 
C, 70.58; H, 3.73; N, 15.24. Found: C, 70.19; H, 3.11; 
N, 15.21%.

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