Synthesis of a novel heterocyclic scaffold utilizing 2-cyano-*N*-(3-cyano-4,6-dimethyl-2-oxopyridin-1-yl) acetamide

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Abstract

2-Cyano-*N*-(3-cyano-4,6-dimethyl-2-oxopyridin-1-yl)acetamide (**3**) was prepared via two routes and its reactions with various aldehydes and diazonium salts were studied. When compound **3** was treated with arylidenemalononitrile in either ethanol or dioxane using piperidine as a catalyst in a trial to prepare bispyridone derivatives **7**, there was no reaction and the reason for this was investigated using molecular modeling. Furthermore, coumarin derivatives **9** and **10** were prepared by reaction of acetamide **3** with salicylaldehyde derivatives. Finally, aminopyrazole derivatives **15** were synthesized by reaction of acetamide **3** with *N,N*-dimethylformamide dimethyl acetal (DMFDMA) then with hydrazine derivatives and their mechanisms was discussed.

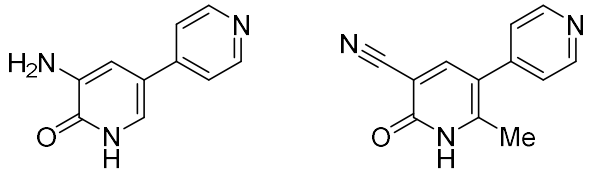
Keywords: Cyanoacetamides, pyrazolyl pyridine, coumarinyl pyridine, hydrazine, reaction modeling, *E/Z* enaminone

Introduction

The pyridine nucleus is of considerable value to chemists and biologists because it occurs in many natural substances and also in a wide array of biologically active molecules. Polyfunctional pyridines are extensively used in heterocyclic synthesis because of their high reactivity as synthons.[1-3]

2-Pyridones are an important subcategory of pyridines that have various biological activities. 2-Pyridone derivatives have appeared as vital backbones in over 7000 surviving drugs.[4,5] In particular, 2-pyridones comprising H-bond acceptor substituent in position-5 establish a relatively new class of specific phosphodiesterase 3 (PDE3) inhibitors,[6] which are used as unconventional alternatives to classic digitalis glycosides for the treatment of congestive heart failure (CHF) *i.e.* amrinone[7] and milrinone[8] (Fig. 1). Substituted pyridones and their dihydro/tetrahydro-derivatives

are present in many natural alkaloids and compounds with these structural styles exhibit important biological properties.[9]



Amrinone Milrinone

Figure 1. Chemical structures of amrinone and milrinone.

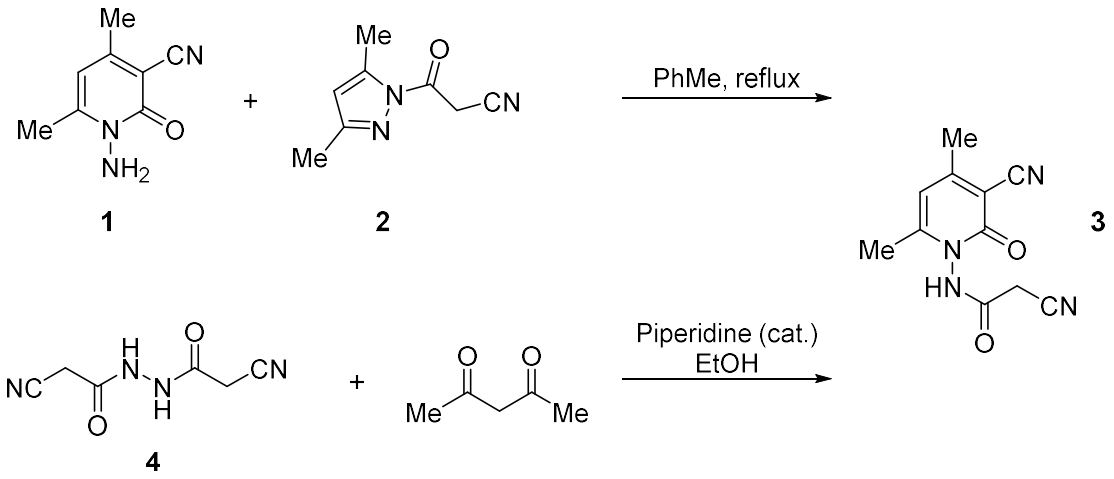
Compounds containing the 2-pyridone motif show a wide range of biological profiles that includes antitumor,[10] antifungal,[11] antibacterial,[12] anti-inflammatory,[13] antiviral,[14] and antithrombotic properties.[15] Also, 2-pyridones are one of unique pharmacophore class, which are found in various therapeutic ligands.[16-18] These heterocycles have attracted great attention due to their uses as drug candidate for instance as a promising candidate for HIV-1 nonnucleoside reverse transcriptase inhibitors (NNRTIs),[19,20] as antifungal agents,[21] and as sedatives.[22]

Moreover, such compounds have recently become valuable because of their similarity to nucleoside structures.[23-27] For all of these advantages related to pyridine moiety and continued to our work,[28-33] we report herein the synthesis and reaction modeling of new library of novel substituted 1-aminopyridine cyanoacetamide derivatives.

Results and Discussion

Our approach toward the policy and progress of new compounds involves the use of 2-cyano-*N*-(3-cyano-4,6-dimethyl-2-oxopyridin-1(2*H*)-yl)acetamide **3** that contains a number of chemically distinct functionalities, which can be reacted with different aldehydes, diazonium salts and *N,N*-dimethylformamide dimethyl acetal (DMFDMA) to generate molecular diversity Scheme 1-3.

The quest for synthesis of 2-cyano-*N*-(3-cyano-4,6-dimethyl-2-oxopyridin-1(2*H*)-yl)acetamide (**3**) was accomplished via two routes (Scheme 1). In the first route, 1-amino-4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (**1**), prepared according to the literature,[34,35] was reacted with 3,5-dimethyl-1*H*-pyrazol-1-yl-3-oxopropanenitrile (**2**) using toluene as a solvent to yield the desired product **3**. In the second method, 2-cyano-*N*′-(2-cyanoacetyl)acetohydrazide (**4**) was reacted with acetylacetone in ethanol in the presence of piperidine to afford the desired product **3**. The yields of the products were achieved in the range of 76-90%. The chemical structure of compound **3** was characterized by IR and $^{1}H/^{13}C$ NMR spectroscopy, as well as by mass spectrometry techniques. The ^{1}H NMR showed two new peaks at 11.48 and 3.38 ppm due to NH and methylene groups, respectively and the absence of a singlet signal at 6.1 ppm due to NH_2 present in compound **1**.



Scheme 1. Synthetic routes to 2-cyano-*N*-(3-cyano-4,6-dimethyl-2-oxopyridin-1(2*H*)-yl)acetamide (**3**).

The reactivity of methylene group was tested by reaction of compound **3** with different aldehydes. This reaction was carried out in alcohol and in presence of piperidine as a catalyst at reflux temperature to afford the arylidine derivatives **5a-h** in very good yields. The structures of compound **5** were characterized by ^{1}H NMR, which showed an increase in the aromatic region signals and the disappearance of a singlet signal at 3.38 ppm corresponding to the disappearance of methylene protons. Also, mass spectrometry confirmed the proposed structures of these compounds (Scheme 2).

When compound **3** was treated with arylidenemalononitrile **6a-g**, in either ethanol or dioxane containing piperidine, in a trial to prepare bispyridone derivative the *m/z* recorded at 230.01 of the isolated product ruled out this assumption. The reason for that was investigated by using molecular modeling which showed that the basicity of pyridone NH is very low (Mulliken charge of -0.443 *vs* -0.766 for the corresponding aniline) (Fig. 2). We thought that Michael addition could be occur due to the depicted Mulliken charges on the methine carbons -0.151 and 0.138 for pyridone but piperidine did not have sufficient basicity to activate the cyclization.

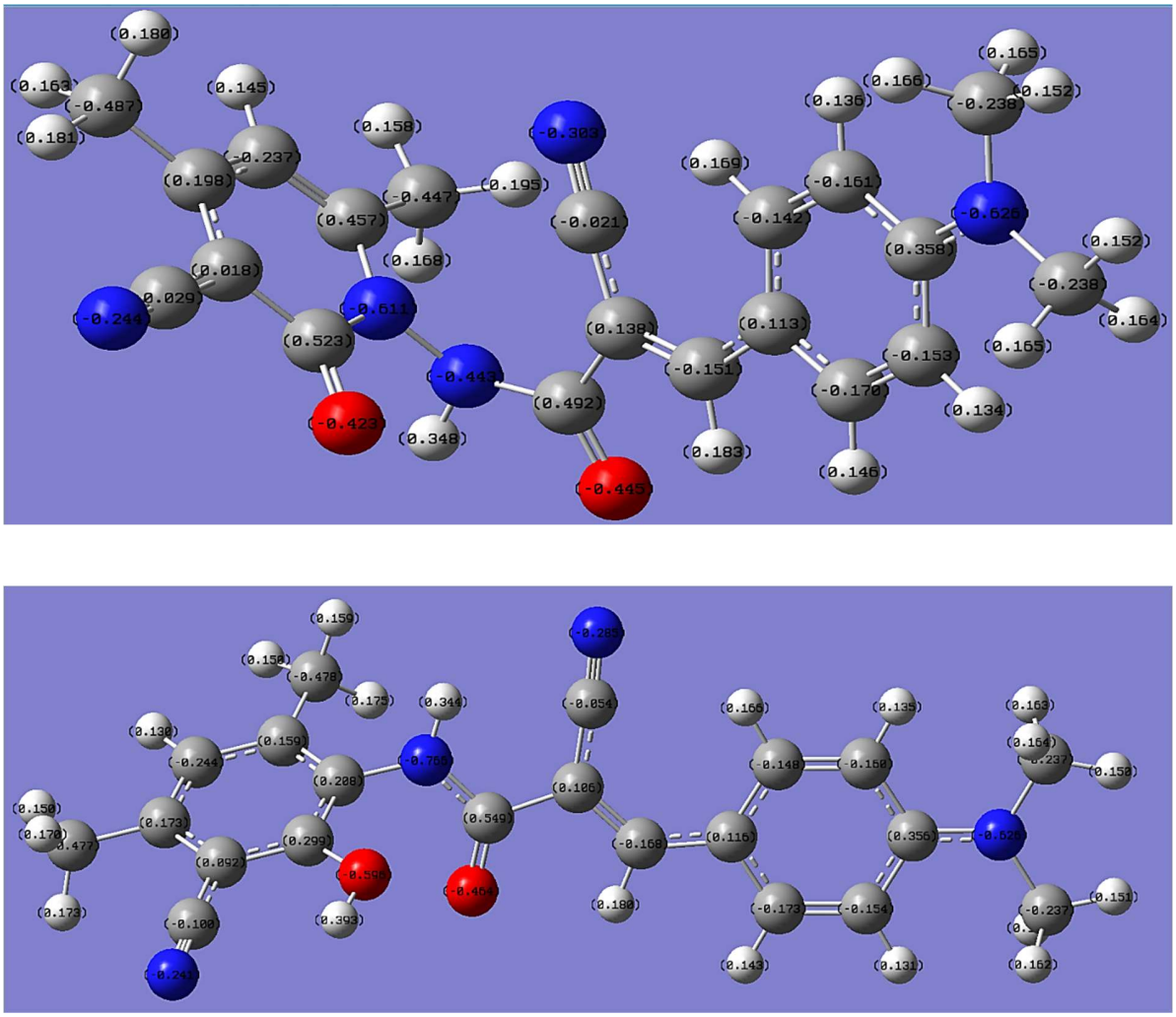
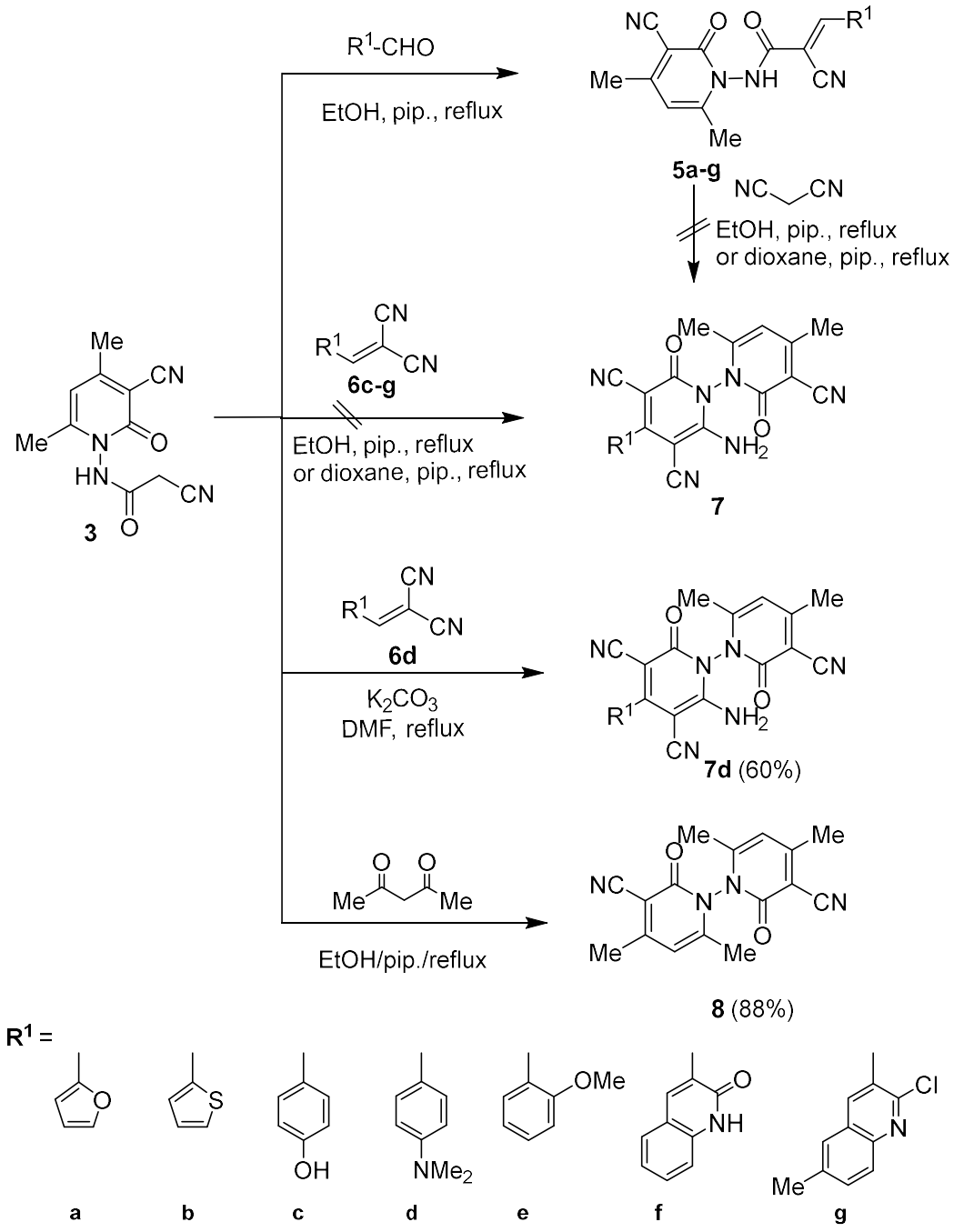


Figure 2. Muliken charges on pyridone and on corresponding aniline.

To evaluate our molecular modeling result, compound **3** was reacted with 2-[4-(dimethylamino)benzylidene]malononitrile (**6d**) in DMF in the presence of K_2CO_3 as a stronger base at reflux. The isolated product was supported to be compound **7d** (60% yield), according to IR spectroscopy that showed new peaks at 3210 and 3221 cm^{-1} due to NH_2. ^1H NMR spectroscopy also showed a new singlet signal at 6.62 ppm corresponding to NH_2 and disappearance a singlet signal at 3.38 ppm. Additional chemical support was obtained by reaction of compound **3** with acetyl acetone in ethanol containing few drops of pipreidine at reflux temperature to afford bispyridone **8** in 88% yield.

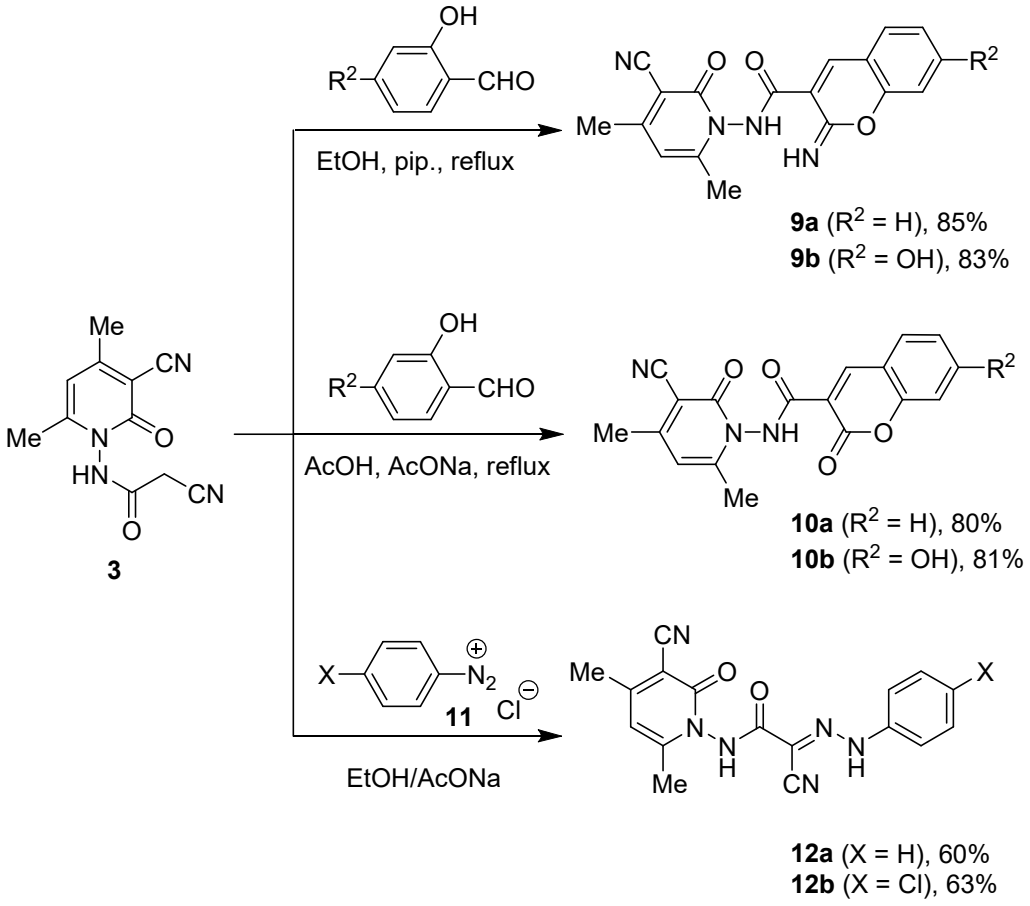


Scheme 2. Synthesis of arylidine derivatives **5a-g** and bispyridones **7d** and **8.**

Because of the biological importance of coumarin derivatives, some new coumarin derivatives **9** and **10** were synthesized from the reaction of compound **3** with salicylaldehyde derivatives in either ethanol containing piperidine or in acetic acid containing anhydrous sodium acetate, respectively. The structure of compounds **9a** and **9b** were supported by IR spectroscopy that

showed new strong peaks at 3340 and 3310 cm^{-1}, respectively attributed to NH stretches. In addition ^1H NMR spectroscopy showed an increase in the intensity of the aromatic signals, appearance of new signals at δ 10.69 and 10.49 ppm because of the new NH and disappearance of methylene protons at δ 3.38 ppm. The structure of compounds **10a** and **10b** was also supported by IR spectroscopy, which showed new strong peaks at 1720 and 1710 cm^{-1}, respectively due to the C=O of coumarin. ^1H NMR spectroscopy also showed an increase in the intensity of the aromatic signals and disappearance of methylene protons at δ 3.38 ppm. The mass spectra of compounds **9** and **10** also gave the anticipated molecular ion peaks (*c.f.* experimental section).

Another test for the reactivity of methylene group was carried out by using it as a coupler with diazonium salts. The reactions with phenyl- or 4-chlorophenyl diazonium chloride were performed in a mixture of ethanol and sodium acetate at 0-5 °C and gave only single products identified as the hydrazo compounds **12a** (X = H) and **12b** (X = Cl) in 60 and 63% yields, respectively. ^1H NMR spectroscopy showed two singlet signals at δ 11.12, 12.32 ppm and 11.19, 12.37 ppm due to 2NH functions of **12a** and **12b**, respectively. In addition, disappearances a singlet signal at δ 3.38 ppm of CH_2 group. IR spectroscopy showed also new peaks at 3323-3230 cm^{-1} belonging to NH stretches. The mass spectra of compounds **12a** and **12b** also gave molecular ion peaks at *m/z* 334 and 368, respectively (Scheme 3).



Scheme 3. Synthesis of coumarin derivatives **9** and **10** and hydrazo derivatives **12.**

Compound **3** was treated with dimethylformamide dimethylacetal (DMFDMA) in refluxing xylene to afford enaminonitrile **13** in 87% yield. Beside the two C=O *str* bands at ≈ 1690 and 1670 cm^{-1} and the C≡N *str* band at 2220 and 2198 cm^{-1}, the NMe_2 protons (^1H NMR) appeared as one singlet signal at δ 3.27 ppm and the olefinic proton was observed as singlet signal at δ 7.8 ppm. The stereochemistry of the enaminonitrile **13** was checked by the Spartan program using the DFT method (B3LYP) which revealed the *Z*-form to be the most stable configuration. This deduction was different from the reported related work.[36] In addition, the calculated heat of formation of the *Z* isomer of **13** is 0.5 kJ/ mole lower than that for the *E* isomer, which is too small, thus both configurations *Z/E* is present in almost equal amount (Fig. 3).

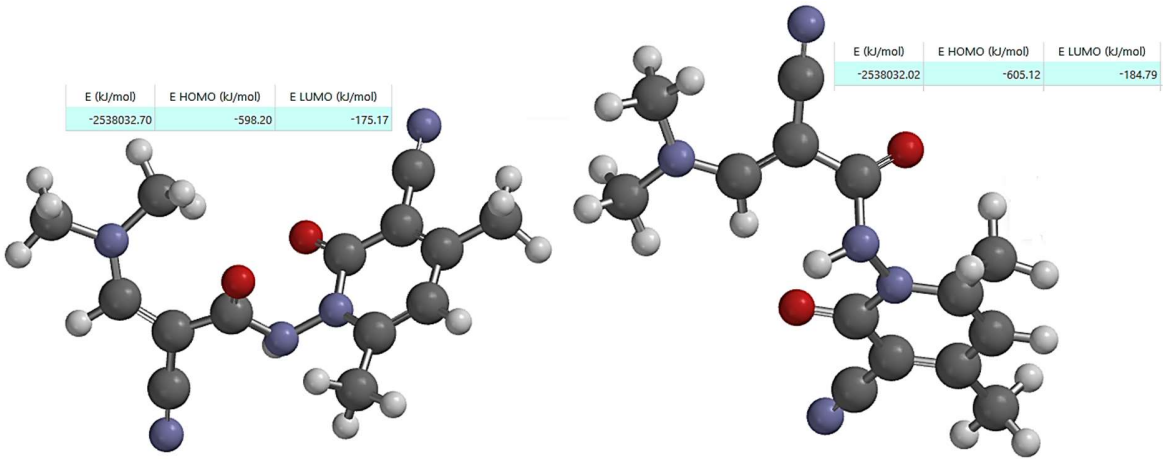
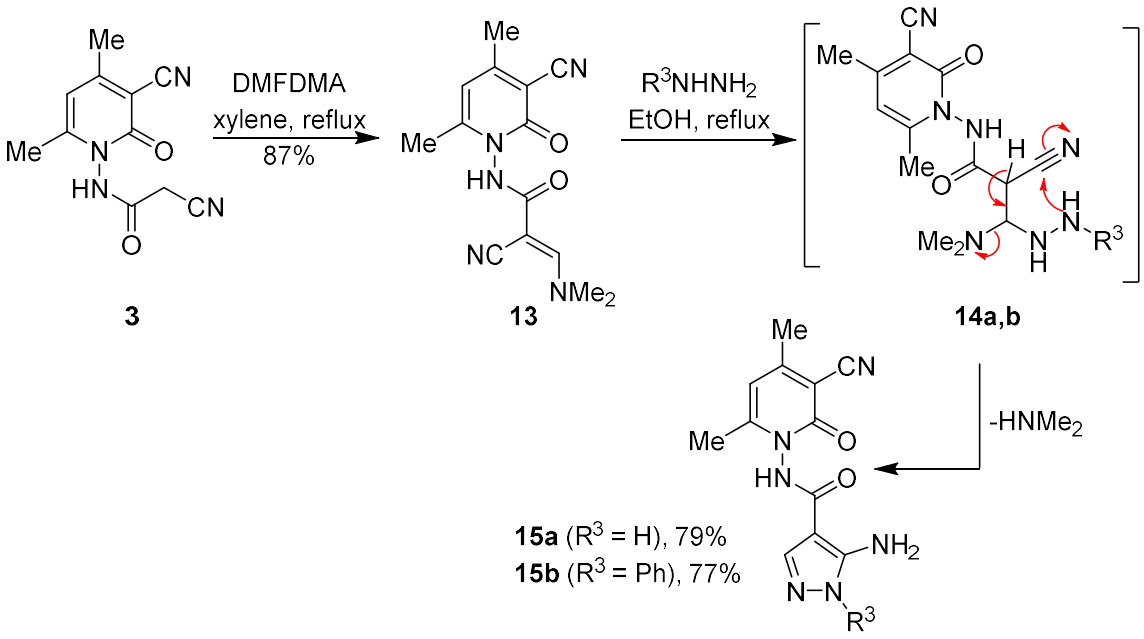


Figure 3. The optimized *E/Z* structures with their E, HOMO and LUMO values.

Cyclocondensation of enaminonitrile **13** with R^3NHNH_2 in EtOH at reflux afforded amino pyrazoles **15** in over 78% yields. A conceivable mechanism for the formation of compounds **15** is proposed in Scheme 3. The reaction proceeded through Michael addition, that subsequently underwent intramolecular nucleophilic attack on cyano carbon followed by annulation to give intermediate **14**, which was transformed to the concluding compound by intramolecular electron transfer to nitrogen atom. Compound **15a** showed a band at 3288 cm^{-1} corresponding to the NH_2 *str.* with concurrent disappearance of the nitrile band and the olefinic singlet (^1H NMR) at $\delta \approx$ 7.8 ppm. In addition, D_2O exchangeable signal appeared at δ 5.97 ppm due to NH_2. Its mass spectrum displayed a molecular ion peak resultant to its correct molecular formula (Scheme 4).



Scheme 4. Synthesis of amino pyrazole derivatives **15a,b**.

Experimental Section

General. All melting points were determined on digital Gallen-Kamp MFB-595 instrument using open capillary tubes and are uncorrected. IR spectra were recorded on Schimadzu FTIR 440 spectrometer using KBr pellets. Mass spectra were performed at 70 eV on an MS-50 Kratos (A.E.I.) spectrometer provided with a data system. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker model (500 MHz) Ultra Shield NMR spectrometer in DMSO-d_6 using tetramethylsilane (TMS) as an internal standard; chemical shifts are reported as δ ppm units. The elemental analyses (% C, H, N) were done at the Microanalytical Center, Cairo University, Cairo, Egypt. The appropriate precautions in handling moisture-sensitive compounds were taken. Solvents were dried by standard techniques. The monitoring of the progress of all reactions and homogeneity of the synthesized compounds was carried out and was run using thin layer chromatography (TLC) aluminum sheets silica gel 60 F_{254} (Merck).

2-Cyano-*N*-(3-cyano-4,6-dimethyl-2-oxopyridin-1(2*H*)-yl)acetamide (3)

Method A. A mixture of 1-amino-4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (**1**) (3.26 g, 20 mmol) and 3,5-dimethyl-1-cyanoacetylpyrazole (**2**) (3.26 g, 20 mmol) in toluene (30 mL) was heated at reflux for 10 min. The reaction mixture was allowed to cool and the resulting precipitate was filtered, washed (toluene), dried, and finally recrystallized to give the *title compound* **3** as colorless plates, yield 4.14 g (90%), mp 170-171 °C (toluene); IR (ν_{max}, cm^{-1}): 3232w (NH), 2223m (CN), 1716s, 1680s (2C=O), 1654s (C=C); ^{1}H NMR (500 MHz, DMSO-d_6)

δ_H (ppm): 2.19 (s, 3 H, CH_3), 2.33 (s, 3H, CH_3) 3.38 (s, 2 H, CH_2) 6.14 (s, 1 H, H5 pyridone) 11.48 (s, D_2O exchangeable, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 18.3 (CH_3), 20.2 (CH_3), 24.0 (CH_2), 100.0 (C3), 108.4 (C5), 115.0 (CN pyridone), 116.1 (CN acetamide), 151.4 (C6), 157.8 (C4), 160.3 (C2), 162.6 (C=O acetamide); MS *m/z* (%): 230.05 [M^+] (35), 163.05 (100). Anal. Calcd. for $C_{11}H_{10}N_4O_2$ (230.23): C, 57.39; H, 4.38; N, 24.34. Found: C, 57.10; H, 4.40; N, 23.98%.

Method B. A mixture of 2-cyano-*N*′-(2-cyanoacetyl)acetohydrazide (**4**) (0.166 g, 1 mmol) and acetylacetone (0.10 g, 1 mmol) in ethanol (20 mL, 95%) containing few drops of piperidine was refluxed for 4 h (TLC). The resulting precipitate was filtered off to give compound **3**.

General procedure for Synthesis 5. To a mixture of **3** (0.23 g, 1 mmol), and appropriate aldehydes **2a-h** (1 mmol) in EtOH (20 mL) few drops of piperidine were added, the reaction mixture was heated under reflux form 3-6 h (TLC). The precipitate formed was collected by filtration, dried, washed with EtOH, and recrystallized from EtOH to afford compounds **5a-g**.

2-Cyano-*N*-(3-cyano-4,6-dimethyl-2-oxopyridin-1(2*H*)-yl)-3-(fur-2-yl)acrylamide (5a). Brown powder, yield 0.277 g (90%), mp 189-190 ºC (EtOH); IR (ν_{max}, cm^{-1}): 3222w (NH), 2214m (C≡N), 1670s (C=O), 1674 s(C=O), 1593s (aromatic C=C); ^{1}H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 2.31 (s, 3H, CH_3), 2.33 (s, 3H, CH_3), 6.34 (s, 1H, H5 pyridone), 6.68 (dd, 1H, *J* 3.5 Hz, 1.5 Hz, furyl-H), 7.53 (d, 1H, *J* 3.5 Hz, furyl-H), 7.78 (d, 1H, *J* 3.5 Hz, furyl-H), 8.21 (s, 1H, =CH), 9.95 (s, D_2O, exchangeable, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 14.3 (CH_3), 16.2 (CH_3), 97 (C-CN acetamide), 99.1 (C-CN ring), 118.1 (C5), 120.9 (C4-furan), 129.2 (CN pyridone), 129.6 (CN, acetamide), 130.1 (C3-furan), 134.0 (C2-furan), 136.8 (C5-furan), 157.7 (C4), 141.3 (C2), 157.7 (C2-pyridone) 164.2 (C=O acetamide); MS *m/z* (%): 308.3 [M^+] (45). Anal. Calcd. for $C_{16}H_{12}N_4O_3$ (308.3): C, 62.33; H, 3.92; N, 18.17. Found: C, 62.20; H, 4.11; N, 17.95%.

2-Cyano-*N*-(3-cyano-4,6-dimethyl-2-oxopyridin-1(2*H*)-yl)-3-(thien-2-yl)acrylamide (5b). Green powder, yield 298 g (92%), mp 195-197 ºC (EtOH); IR (ν_{max}, cm^{-1}): 3220w (NH), 2216m (C≡N), 1674s (C=O), 1667s (C=O), 1593s (aromatic C=C); ^{1}H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 2.30 (s, 3 H, CH_3), 2.34 (s, 3 H, CH_3), 6.36 (s, 1H, H5 pyridone), 7.15 (dd, 1H, *J* 4.8 Hz, 3.8 Hz, thienyl-H), 7.49 (d, 1H, *J* 2.9 Hz, thienyl-H), 7.88 (d, 1H, *J* 3.9 Hz, thienyl-H), 8.14 (s, 1H, =CH), 9.95 (s, D_2O exchangeable, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 14.3 (CH_3), 16.2 (CH_3), 97.0 (C-CN acetamide), 99.1 (C-CN ring), 118.1 (C5), 120.9 (C4-furan), 129.2 (CN pyridone), 129.6 (CN, acetamide), 130.1 (C3-furan), 134.0 (C2-furan), 136.8 (C5-furan), 157.7 (C4), 141.3 (C2), 157.7 (C2-pyridone) 164.2 (C=O, acetamide); MS *m/z* (%): 324 [M^+] (18), 163 (100); Anal. Calcd. for $C_{16}H_{12}N_4O_2S$ (324.36): C, 59.25; H, 3.73; N, 17.27. Found: C, 59.41; H, 3.81; N, 17.41%.

2-Cyano-*N*-(3-cyano-4,6-dimethyl-2-oxopyridin-1(2*H*)-yl)-3-(4-hydroxyphenyl)acrylamide (5c). Colorless microcrystals, yield 0.307 g (92%), mp 290 ºC (EtOH); IR (ν_{max}, cm^{-1}): 3332m (OH), 3209w (NH), 2222s (C≡N), 1670s (C=O), 1647s (C=O), 1614s (aromatic C=C); ^{1}H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 2.32 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 6.40 (s, 1H, H5 pyridone), 6.93 (d, 2H, *J* 8.5 Hz, Ar-H), 7.78 (d, 2H, *J* 8.5 Hz, Ar-H), 8.63 (s, 1H, =CH), 9.79 (s, D_2O

exchangeable, 1H, OH), 10.42 (s, D_2O exchangeable, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 18.5 (CH_3), 19.5 (CH_3), 99.4 (C-CN ring), 107.7 (C-CN acetamide), 107.8 (C5), 115.8 (CN pyridone), 116.0 (C3, C5-Ar), 122.8 (CN acetamide), 131.2 (C1-Ar), 132.1 (C2, C6- Ar), 150.8 (C6- pyridone), 151.4 (CH=), 156.8 (C4-pyridone), 162.0 (C2-pyridone), 163.3 (C4-Ar) 170.1 (C=O, acetamide); MS *m/z* (%): 334 [M^+] (10), 303 (13), 163 (22), 148 (100); Anal. Calcd. for $C_{18}H_{14}N_4O_3$ (334.3): C, 64.67; H, 4.22; N, 16.76. Found: C, 64.55; H, 4.41; N, 16.59%.

2-Cyano-*N*-(3-cyano-4,6-dimethyl-2-oxopyridin-1(2*H*)-yl)-3-[(4-dimethylamino)phenyl]-acrylamide (5d). Red powder, yield 0.328 g (91%), mp 260 °C (EtOH); IR (ν_{max}, cm^{-1}): 3346w (NH), 2212m (C≡N), 1653m (C=O), 1640s (C=O), 1590s (aromatic C=C); ^1H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 2.25 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), .311 (s, 6H, $2CH_3$), 6.53 (s, 1H, H5 pyridone), 6.77 (d, 2H, *J* 8 Hz, Ar-H), 7.88 (d, 2H, *J* 8, Ar-H), 8.01 (s, 1H, =CH), 8.60 (s, D_2O exchangeable, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 18.7 (CH_3), 20.0 (CH_3), 41.9 ($2CH_3$), 105.0 (C-CN ring), 107.9 (C-CN acetamide), 110.8 (C5), 112.0 (C3,C5, Ar), 116.9 (CN, pyridone), 121.2 (C1-Ar), 123.8 (CN, acetamide), 132.6 (C2,C4, Ar), 141.4 (C6-pyridone), 149.3 (CH=), 151.5 (C6, Ar), 154.3 (C4-pyridone), 160.3 (C2-pyridone), 165.3 (C=O, acetamide); MS *m/z* (%): 361 [M^+] (5), 163 (55), 146 (100); Anal. Calcd. for $C_{20}H_{19}N_5O_2$ (361.4): C, 66.47; H, 5.30; N, 19.38. Found: C, 66.28; H, 5.41; N, 19.43%.

2-Cyano-*N*-(3-cyano-4,6-dimethyl-2-oxopyridin-1(2*H*)-yl)-3-(2-methoxyphenyl)acrylamide (5e). Yellow powder, yield 0.309 g (89%), mp 205-206 °C (EtOH); IR (ν_{max}, cm^{-1}): 3432w (NH), 2212m (C≡N), 1670s (C=O), 1649s (C=O), 1612s (aromatic C=C); ^1H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 2.27 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 6.78 (s, 1H, H5 pyridone), 7.01-7.16 (m, 1H, Ar-H), 7.35-7.47 (m, 1H, Ar-H), 7.36 (d, 1 H, *J* 7.9 Hz, Ar-H), 7.83 (d, 1H, *J* 8 Hz, Ar-H), 8.12 (s, 1H, =CH), 9.13 (s, D_2O exchangeable, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 17.3 (CH_3), 19.9 (CH_3), 54.3 (O-CH_3), 103.4 (C-CN ring), 108.9 (C-CN acetamide), 112.0 (C5), 114.0 (C3, Ar), 117.0 (CN pyridone), 120.8 (CN acetamide), 122.2 (C1-Ar), 123.7 (C5-Ar), 128.1 (C4, Ar), 130.2 (C6, Ar), 140.7 (C6- pyridone), 149.4 (CH=), 153.8 (C4-pyridone), 160.3 (C2-pyridone), 160.3 (C2-Ar) 166.1 (C=O, acetamide); MS *m/z* (%): 348. [M^+] (74), 163 (100); Anal. Calcd. for $C_{19}H_{16}N_4O_3$ (348.36): C, 65.51; H, 4.63; N, 16.08. Found: C, 65.36; H, 4.56; N, 15.97%.

2-Cyano-*N*-(3-cyano-4,6-dimethyl-2-oxopyridin-1(2*H*)-yl)-3-(2-oxo-1,2-dihydroquinolin-3-yl)acrylamide (5f). Yellow powder, yield 0.346 (90%), mp >300 °C (EtOH); IR (ν_{max}, cm^{-1}): 3449w (NH), 3163w (NH), 2218m (C≡N), 1672s, 1660s, 1640s (3C=O), 1593w (aromatic C=C); ^1H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 2.37 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 6.43 (s, 1H, H5 pyridone), 7.28 (dd, 1H, *J* 7, 7.50 Hz, quinoline-H), 7.39 (d, 1H, *J* 8.5 Hz, quinoline-H), 7.63-7.67 (dd, 1 H, *J* 8, 8.5 Hz, quinoline-H), 7.92 (d, 1H, *J* 7.5, quinoline-H), 7.96 (s, 1H, =CH), 8.80 (s, D_2O exchangeable, 1H, NH), 8.82 (s, D_2O exchangeable, 1H, NH), 8.99 (s, 1H, H4 quinoline); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 19.6 (CH_3), 20.5 (CH_3), 99.8 (C-CN ring), 101.7 (C-CN acetamide), 108.0 (C5), 115.4 (CN pyridone), 115.8 (C8-quinoline), 118.5 (C9-quinoline), 122.6 (CN acetamide), 123.0 (C6 quinoline), 130.0 (C3-quinoline), 132.9 (C5-quinoline), 139.5 (C7-quinoline), 140.4 (C6-pyridone), 150.8 (C10-quinoline), 156.8 (C4-quinoline), 157.4 (C-methin),

160.6 (C2-quinoline), 162.8 (C2-pyridone), 165.3 (C4-Ar) 168.1 (C=O acetamide); MS *m/z* (%): 385 [M^+] (47), 163 (100); Anal. Calcd. for $C_{21}H_{15}N_5O_3$ (385.3): C, 65.45; H, 3.92; N, 18.17. Found: C, 65.42; H, 3.89; N, 18.24%.

3-(2-Chloro-6-methylquinolin-3-yl)-2-cyano-*N*-(3-cyano-4,6-dimethyl-2-oxopyridin-1(2*H*)-yl)acrylamide (5g). Green powder, yield 0.376 g (90%), mp 295 °C (EtOH); IR (ν_{max}, cm^{-1}): 3290w (NH), 2216m, 2220m (C≡N), 1690s, 1666s (2C=O), 1610s (aromatic C=C); ^{1}H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 2.21 (s, 3 H, CH_3), 2.31 (s, 3H, CH_3), 2.54 (s, 3H, CH_3), 6.69 (s, 1 H, H5 pyridone), 7.37 (s, 1H, quinoline-H), 7.75 (d, 1H, *J* 8.5 Hz, quinoline-H), 7.92 (d, 1H, *J* 8.5 Hz, quinoline-H), 8.13 (s, 1H, =CH), 8.98 (s, 1H, quinoline-H4), 9.32 (s, D_2O exchangeable, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 18.9 (CH_3), 20.9 (CH_3), 21.8 (CH_3), 109.1, 112.1, 115.4, 115.9, 117.2, 125.3, 128.0, 129.9, 132.1, 133.3, 135.9, 145.0, 158.4, 149.0, 151.7, 154.3, 161.2, 165.1; MS *m/z* (%): 417 [M^+] (15), 419 [M^+] (5), 163 (100). Anal. Calcd. for $C_{22}H_{16}ClN_5O_2$ (417.8): C, 63.24; H, 3.86; N, 16.76. Found: C, 63.19; H, 3.81; N, 16.66%.

6-Amino-4-[4-(dimethylamino)phenyl]-4',6'-dimethyl-2,2'-dioxo-2*H*,2'*H*-(1,1'-bipyridine)-3,3',5-tricarbonitrile (7d). To a solution of compound **3** (0.230 g, 1 mmol) and 2-(4-(dimethylamino)benzylidene)malononitrile **6d** (0.198 g, 1 mmol) in DMF (10 mL), anhydrous potassium carbonate (0.69 g, 5 mmol) was added and the reaction mixture was heated at reflux for 5 h (TLC). The reaction mixture was then cooled to room temperature and poured onto ice-water then acidified with acetic acid. The resulting precipitate was filtered, washed well with water and recrystallized to afford the *title compound* **7d**. Brown powder, yield 0.255 g (60%), mp >300 °C (EtOH/DMF, 1:1); IR (vmax, cm^{-1}):3221w, 3210w (NH_2), 2222-2220m (C≡N), 1677s (2C=O), 1606s (aromatic C=C); ^{1}H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 2.24 (s, 3H, CH_3), 2.33 (s, 3H, CH_3), 3.12 (s, 6H, $2CH_3$), 6.24 (s, 1H, H5 pyridone), 6.62 (s, D_2O exchangeable, 2H, NH_2), 6.92 (d, 2H, *J* 8.5, Ar-H), 7.48 (d, 2H, *J* 8.5, Ar-H); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 18.7 (CH_3), 21.4 (CH_3), 40.2 ($2CH_3$), 77.3, 109.1, 110.4, 115.0, 115.4, 117.2, 122.0, 129.1, 133.1, 145.0, 150.2, 158.4, 159.0, 161.0, 170.1; MS *m/z* (%): 425 [M^+] (13), 147 (100); Anal. Calcd. for $C_{23}H_{19}N_7O_2$ (425.45): C, 64.93; H, 4.50; N, 23.05. Found: C, 65.12; H, 4.62; N, 22.97%.

4,4',6,6'-Tetramethyl-2,2'-dioxo-2*H*,2'*H*-[1,1'-bipyridine]-3,3'-dicarbonitrile (8). A mixture of **3** (0.230 g, 1 mmol), and acetyl acetone (0.01g, 1 mmol) in EtOH (20 mL) containing few drops of piperidine was heated at reflux for 5 h (TLC). The precipitate formed was collected by filtration, washed (EtOH), and recrystallized to give the title compound **8** as colorless crystals, yield 0.258 g (88%), mp >300 °C (EtOH), lit.[37] mp 303-304.5 °C, IR (ν_{max}, cm^{-1}): 2222s (C≡N), 1681s (2C=O), 1606s (aromatic C=C); ^{1}H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 2.27 (s, 6H, 2 CH_3), 2.38 (s, 6 H, $2CH_3$), 6.64 (s, 2H, H5, pyridine-H); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 18.2 (CH_3), 22.0 (CH_3), 108.8, 115.5, 117.6, 133.4, 144.7, 159.8; MS *m/z* (%): 163 [M^+ - (C_8H_5NO)] (100), 147 [M^+ - ($C_8H_7N_2O$)] (17), 134 [M^+ - ($C_9H_9N_2O$)] (65); Anal. Calcd. for $C_{16}H_{14}N_4O_2$ (294.3): C, 65.30; H, 4.79; N, 19.04. Found: C, 65.28; H, 4.82; N, 19.12%.

General procedure for Synthesis of coumarins 9a and 9b. A mixture of cyanoacetamide **3** (0.46 g, 2 mmol) and salicylaldehyde (0.244 g, 2 mmol) or 2,4-dihydroxybenzaldehyde (0.276 g, 2 mmol) in EtOH (25 mL) containing a catalytic amount of piperidine was heated under reflux for 4 h (TLC), then left to cool. The solid product formed was filtered off, washed with EtOH, dried, and finally recrystallized from dioxane to give **9a** and **9b**, respectively.

***N*-(3-Cyano-4,6-dimethyl-2-oxopyridin-1(2*H*)-yl)-2-imino-2*H*-chromene-3-carboxamide (9a)**. Brown microcrystalline, yield 0.568 g (85%), mp 190-191 °C (dioxane); IR (ν_{max}, cm^{-1}): 3340w, 3292w (2NH), 2223m (C≡N), 1720s, 1660s (2C=O), 1600s (C=N), 1568s (C=C); ^{1}H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 2.30 (s, 3 H, CH_3), 2.36 (s, 3 H, CH_3), 6.38 (s, 1 H, H5 pyridone), 6.93 (dd, 1H, H6 coumarin), 7.44 (d, 1H, *J* 7.6 Hz, H8 coumarin), 7.58 (dd, 1 H, H7 coumarin), 7.95 (d, 1H, *J* 7.5, H5 coumarin), 9.01 (s, 1H, H4 coumarin), 10.69 (s, D_2O exchangeable, 1H, NH), 11.14 (s, D_2O exchangeable, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 20.2 (CH_3), 21.0 (CH_3), 108.4, 116.7, 117.7, 120.0, 120.2, 125.8, 129.8, 135.0, 135.5, 137.0, 150.2, 154.8, 155.0, 161.3, 168.1, 175.1; MS *m/z* (%): 334 [M^+] (19%), 163 (100); Anal. Calcd. for $C_{18}H_{14}N_4O_3$ (334.3): C, 64.67; H, 4.22; N, 16.76. Found: C, 64.81; H, 4.11; N, 16.69%.

***N*-(3-Cyano-4,6-dimethyl-2-oxopyridin-1(2*H*)-yl)-7-hydroxy-2-imino-2*H*-chromene-3-carboxamide (9b)**. Brown powder, yield 0.580 g (83%), mp 260 °C (dioxane); IR (ν_{max}, cm^{-1}): 3460w (OH), 3310w, 3190w (2NH), 2222w (C≡N), 1703s, 1670s (2C=O), 1604s (C=N), 1581s (C=C); ^{1}H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 2.25 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 6.44 (s, 1 H, H5 pyridone), 6.75 (s, 1H, H8 coumarin), 6.93 (dd, 1H, H6 coumarin), 7.86 (d, 1H, *J* 7.5, H5 coumarin), 9.01 (s, 1H, H4 coumarin), 9.87 (s, D_2O exchangeable, 1H, OH), 10.49 (s, D_2O exchangeable, 1H, NH), 10.84 (s, D_2O exchangeable, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 19.8 (CH_3), 21.0 (CH_3), 109.1, 116.6, 117.8, 121.1, 121.7, 126.5, 130.3, 135.0, 136.0, 136.8, 150.8, 154.6, 155.1, 162.1, 168.3, 175.2; MS *m/z* (%): 350 [M^+] (16), 163 (100); Anal. Calcd. for $C_{18}H_{14}N_4O_4$ (350.3): C, 61.71; H, 4.03; N, 15.99. Found: C, 61.68; H, 3.98; N, 16.11%.

General procedure for Synthesis of coumarin 10a,b. To a solution of **3** (0.46 g, 2 mmol) in acetic acid (30 mL) containing 0.5 g of fused sodium acetate, salicylaldehyde (0.244 g, 2 mmol) or 2,4-dihydroxybenzaldehyde (0.276 g, 2 mmol) was added. The mixture was heated under reflux for 3 h (TLC). After cooling, the formed product was filtered off, washed with EtOH, dried, and finally recrystallized from mixture EtOH/DMF (1:1) to give **10a** and **10b**, respectively.

***N*-(3-Cyano-4,6-dimethyl-2-oxopyridin-1(2H)-yl)-2-oxo-2*H*-chromene-3-carboxamide (10a)**. Yellow powder, yield 0.536 g (80%), mp >300 °C; IR (ν_{max}, cm^{-1}): 3296w (NH), 2218m (C≡N), 1720s (C=O, lactone), 1670s, 1663s (2C=O), 1610s (C=C); ^{1}H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 2.29 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 6.38 (s, 1H, H5 pyridone), 7.45 (dd, 1H, H6 coumarin), 7.44 (d, 1H, *J* 7.6 Hz, H8 coumarin), 7.6 (dd, 1H, H7 coumarin), 8.45 (d, 1H, *J* 7.5, H5 coumarin), 9.21 (s, 1H, H4 coumarin), 10.34 (s, D_2O exchangeable, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 20.2 (CH_3), 21.0 (CH_3), 108.4, 116.7, 117.7, 120.0, 120.2, 125.8, 129.8, 135.0, 135.5, 137.0, 150.2, 154.8,155.0, 161.3, 163.2, 166.2; MS *m/z* (%): 335 [M^+] (24), 163

(100); Anal. Calcd. for $C_{18}H_{13}N_3O_4$ (335.3): C, 64.48; H, 3.91; N, 12.53. Found: C, 64.39; H, 3.75; N, 12.61%.

***N*-(3-Cyano-4,6-dimethyl-2-oxopyridin-1(2*H*)-yl)-7-hydroxy-2-oxo-2*H*-chromene-3-carboxamide (10b)**. Brown powder, yield 0.568 g (81%), mp >300 °C; IR (ν_{max}, cm^{-1}): 3306w (OH), 3259w (NH), 2218m (C≡N), 1720s (C=O lactone), 1670s, 1660s (2C=O), 1610m (aromatic C=C); ^{1}H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 2.31 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 6.40 (s, 1H, H5 pyridone), 6.94 (dd, 1H, H6 coumarin), 7.45 (d, 1H, *J* 7.6 Hz, H8 coumarin), 7.97 (d, 1H, *J* 7.5, H5 coumarin), 9.21 (s, 1H, H4 coumarin), 9.87 (s, D_2O exchangeable, 1H, OH), 10.34 (s, D_2O exchangeable, 1H, NH), ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 20.2 (CH_3), 21.0 (CH_3), 108.4, 116.7, 117.7, 120.0, 120.2, 125.8, 129.8, 135.0, 135.6, 136.9, 150.4, 154.7, 155.1, 161.3, 163.0, 166.0; MS *m/z* (%): 351 [M^+] (24), 163 (100). Anal. Calcd. for $C_{18}H_{13}N_3O_5$ (351.3): C, 61.54; H, 3.73; N, 11.96. Found: C, 61.61; H, 3.66; N, 11.89%.

General procedure for synthesis 12. To a stirred solution of compound **3** (0.23 g, 1 mmol) in ethanol (30 mL) sodium acetate trihydrate (0.13 g, 1 mmol) was added. After stirring for 15 min, the mixture was chilled at 0 °C and treated with cold solution of aniline (0.093 g, 1 mmol) or 4-chloroaniline (0.127 g, 1 mmol) in 6 M hydrochloric acid (1.5 mL) with sodium nitrite solution (0.07 g, 1 mmol) in water (3 mL). The reaction mixture was stirred for an additional 2 h at 0–5 °C and then left for 8 h in a refrigerator (4 °C). The resulting solid was collected by filtration, washed thoroughly with water and dried. The crude product was recrystallized from ethanol to give hydrazones **12a** and **12b**, respectively.

2-[(3-Cyano-4,6-dimethyl-2-oxopyridin-1(2*H*)-yl)amino]-2-oxo-*N*-phenylacetohydrazonoyl cyanide (12a). Yellow microcrystalline, yield 0.2 g (60%), mp 270 °C (EtOH); IR (ν_{max}, cm^{-1}): 3315w, 3232w (2NH), 2220m (C≡N), 1693s, 1654s (2C=O), 1595s (aromatic C=C); ^{1}H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 2.31 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 6.46 (s, 1 H, H5 pyridone), 7.2 (t, 1H, Ar-H), 7.42 (t, 2H, Ar-H), 7.74 (d, 2H, *J* 7.5 Hz, Ar-H), 11.12 (s, D_2O exchangeable, 1H, NH), 12.32 (s, D_2O exchangeable, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 20.1 (CH_3), 21.9 (CH_3), 106.7, 109.2, 110.8, 114.9, 115.6, 117.7, 123.0, 130.1, 133.4, 141.2, 154.5, 159.1, 163.6; MS *m/z* (%): 334 [M^+] (5), 163 (100), Anal. Calcd. for $C_{17}H_{14}N_6O_2$ (334.3): C, 61.07; H, 4.22; N, 25.14. Found: C, 60.98; H, 4.12; N, 25.32%.

2-[(4-Chlorophenyl)hydrazono]-2-cyano-*N*-(3-cyano-4,6-dimethyl-2-oxopyridin-1(2*H*)-yl) acetamide (12b). Yellow powder, yield 0.231 g (63%), mp 270 °C (EtOH); IR (ν_{max}, cm^{-1}): 3323w, 3230w (2NH), 2222s (C≡N), 1697s, 1662s (2C=O), 1597w (aromatic C=C); ^{1}H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 2.25 (s, 3H, CH_3), 2.28 (s, 3H, CH_3), 6.43 (s, 1 H, H5 pyridone), 7.45 (d, 2H, *J* 8.6 Hz), 7.72 (d, 2H, *J* 8.6 Hz), 11.19 (s, D_2O exchangeable, 1H, NH), 12.37 (s, D_2O exchangeable, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 19.3 (CH_3), 20.9 (CH_3), 106.7, 109.2, 110.9, 114.9, 116.9, 117.7, 127.8, 129.7, 133.0, 141.2, 154.5, 160.1, 163,4; MS *m/z* (%): 368 [M^+] (3), 370 [$M^+ + 2$] (1), 163 (100); Anal. Calcd. for $C_{17}H_{13}ClN_6O_2$ (368.7): C, 55.37; H, 3.55; N, 22.79. Found: C, 55.22; H, 3.48; N, 22.88%.

2-Cyano-*N*-(3-cyano-4,6-dimethyl-2-oxopyridin-1(2*H*)-yl)-3-(dimethylamino)acrylamide (13). A mixture of the cyanoacetamide **3** (0.46 g, 2 mmol) and dimethylformamide-dimethylacetal (DMFDMA) (0.246 mL, 2 mmol) in dry xylene (20 mL) was heated at reflux for 4 h (TLC), and then allowed to cool. The precipitated product was filtered off, washed with petroleum ether (60/80 ^{o}C), dried, and recrystallized to give the *title compound* **13**. Orange powder, yield 0.496 g (87%), mp 205-206 ^{o}C (toluene); IR (ν_{max}, cm^{-1}): 3298w (NH), 2220m (C≡N), 2198m (C≡N), 1690s (C=O), 1670s (C=O), 1598s (aromatic C=C); ^{1}H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 2.21 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 3.27 (s, 6H, $2CH_3$), 6.32 (s, 1H, H5 pyridone), 7.8 (s, 1H, =CH), 10.13 (s, D_2O exchangeable, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 19.5 (CH_3), 21.2 (CH_3), 43.2, 98.9, 109.4, 114.6, 115.7, 117.6, 133.7, 155.2, 157.0, 161.4, 164.7; MS *m/z* (%): 285 [M^{+}] (67%), 163 (100); Anal. Calcd. for $C_{14}H_{15}N_5O_2$ (285.3): C, 58.94; H, 5.30; N, 24.55. Found: C, 59.11; H, 5.13; N, 24.49%.

General procedure for Synthesis of pyrazoles 15. To a solution of enaminonitrile **13** (0.57 g, 2 mmol) in EtOH (20 mL), hydrazine hydrate (80%, 0.2 mL, 4 mmol) or phenylhydrazine (0.2 mL, 2 mmol) was added. The mixture was heated at reflux (5 h) (TLC), and then allowed to cool. The precipitated product was filtered, washed (EtOH), dried, and recrystallized from EtOH/DMF (1:1) to give compounds **15a** and **15b**, respectively.

5-Amino-*N*-(3-cyano-4,6-dimethyl-2-oxopyridin-1(2*H*)-yl)-1*H*-pyrazole-4-carboxamide (15a). Brown prisms, yield 0.428 g (79%), mp 169-170 ^{o}C (EtOH/DMF, 1:1); IR (ν_{max}, cm^{-1}): 3288w, 3203w (NH_2, NH), 2222s (C≡N), 1670s, 1664s (2C=O), 1624s (aromatic C=C); ^{1}H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 2.22 (s, 3H, CH_3), 2.33 (s, 3H, CH_3), 5.97 (s, D_2O exchangeable, 2H, NH_2), 6.23 (s, 1 H, H5 pyridone), 7.64 (s, 1H, H3 pyrazole), 8.92 (s, D_2O exchangeable, 1H, NH), 11.13 (s, D_2O exchangeable, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 18.3 (CH_3), 21.2 (CH_3), 109.2, 114.7, 116.0, 116.7, 129.4, 134.7, 155.1, 156.2, 161.4, 163.7; MS *m/z* (%): 272 [M^{+}] (60%), 163 (100); Anal. Calcd. for $C_{12}H_{12}N_6O_2$ (272.3): C, 52.94; H, 4.44; N, 30.87. Found: C, 52.88; H, 4.36; N, 30.75%.

5-Amino-*N*-(3-cyano-4,6-dimethyl-2-oxopyridin-1(2*H*)-yl)-1-phenyl-1*H*-pyrazole-4-carboxamide (15b). Brown prisms, yield 0.536 g (77%), mp 167-168 ^{o}C (EtOH/DMF, 1:1); IR (ν_{max}, cm^{-1}): 3260w, 3220w (NH_2, NH), 2220m (C≡N), 1670s, 1664s (2C=O), 1624s (aromatic C=C); ^{1}H NMR (500 MHz, DMSO-d_6) δ_H (ppm): 2.21 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 6.17 (s, D_2O exchangeable, 2H, NH_2), 6.32 (s, 1H, H5 pyridone), 7.47 (d, 2H, *J* 7.59 Hz), 7.54-7.58 (m, 3H, Ar-H), 7.67 (s, 1H, H3 pyrazole), 9.42 (s, D_2O exchangeable, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C (ppm): 17.8 (CH_3), 20.8 (CH_3), 109.2, 114.7, 116.0, 116.6, 123.5, 126.2, 129.4, 131.5, 134.7, 138.2, 155.1, 156.2, 161.4, 163.7; MS *m/z* (%): 348 [M^{+}] (57), 163 (100); Anal. Calcd. for $C_{18}H_{16}N_6O_2$ (348.37): C, 62.06; H, 4.63; N, 24.12. Found: C, 62.18; H, 4.36; N, 24.25%.

References

1. Elnagdi, M. H.; Ghozlan, S. A.; Abd-Razik, F. M.; Maghraby, A. S. *J. Chem. Res. Synop.* **1991**, *5*, 116.
2. Attaby, F. A.; Eldin, S. M.; Abd El-Razik, M. *Phosphorus, Sulfur Silicon Relat. Elem.* **1995**, *21*, 106.
3. Krauze, A.; Verhe, R.; Duburs, G. *Khim. Geterotsikl. Soedin.* **1994**, *1*, 139.
4. Li, A. H.; Moro, S.; Forsyth, N.; Melman, N.; Ji, X. D.; Jacobsen, K. A. *J. Med. Chem.* **1999**, *42*, 706. http://dx.doi.org/10.1021/jm980550w
5. Vacher, B.; Bonnand, B.; Funes, F.; Jubault, N.; Koek, W.; Assie, M. B.; Cosi, C.; Kleven, M. *J. Med. Chem.* **1999**, *42*, 1648. http://dx.doi.org/10.1021/jm9806906
6. Dorigo, P.; Gaion, R. M.; Belluco, P.; Fraccarollo, D.; Maragno, I.; Bobieri, G.; Benetoll, F.; Mosti, L.; Orsini, F. *J. Med. Chem.* **1993**, *36*, 2475. http://dx.doi.org/10.1021/jm00069a005
7. Farah, A. E.; Alousi, A. A. *Life Sci.* **1978**, *22*, 1139. http://dx.doi.org/10.1016/0024-3205(78)90083-8
8. Alousi, A. A.; Canter, J. M.; Monterano, M. J.; Fort, D. J.; Ferrari, R. A. *J. Cardiovasc. Pharmacol.* **1983**, *5*, 792. http://dx.doi.org/10.1097/00005344-198309000-00014
9. Paulvannan, K.; Chen, T. *J. Org. Chem.* **2000**, *65*, 6160. http://dx.doi.org/10.1021/jo000676c
10. Daniel, L. F.; Peter, A. P. U.S. Patent 191336, **2007**.
11. Rao, H. S. P.; Senthilkumar, S. P. *Curr. Org. Chem.* **2004**, *8*, 1521. http://dx.doi.org/10.2174/1385272043369881
12. Misic-Vukovic, M.; Mijin, D.; Radojkovic-Velickovic, M.; Valentic, N.; Krstic, V. *J. Serb. Chem. Soc.* **1998**, *63*, 585.
13. Uscumlic, G.; Mijin, D.; Valentic, N.; Vajs, V.; Susic, B. *Chem. Phys. Lett.* **2004**, *397*, 148. http://dx.doi.org/10.1016/j.cplett.2004.07.057
14. Forlani, L.; Gristoni, G.; Boga, C.; Todesco, P. E.; Del Vechio, E.; Salva, S.; Monari, M. *ARKIVOC* **2002**, *11*, 198.
15. Krick-Othmer; Encyclopedia of Chemical Technology, 2nd Ed. Wiley Interscience Publication: New York, 1968; Vol. 15, p 638.
16. Saiki, A. Y. C.; Shen, L. L.; Chen, C. M.; Baranowski, J.; Lerner, C. G. *Antimicrob. Agents Chemother.* **1999**, *43*, 1574.
17. Li, Q.; Mitscher, L. A.; Shen, L. L. *Med. Res. Rev.* **2000**, *4*, 231. http://dx.doi.org/10.1002/1098-1128(200007)20:4<231::AID-MED1>3.0.CO;2-N
18. Brickner, S. *Chem. Ind.* **1997**, 131

19. Goldman, M. E.; Nunberg, J. H.; O'Brien, J. A.; Quintero, J. C.; Schleif, W. A.; Freund, K. F.; Gaul, S. L.; Saari, W. S.; Wai, J. S.; Hoffman, J. M.; Anderson, P. S.; Hupe, D. J.; Emini, E. A.; Stern, A. M. *Proc. Natl. Acad. Sci. U.S.A.* **1991**, *88*, 6863. http://dx.doi.org/10.1073/pnas.88.15.6863
20. Medina-Franco, J. L.; Martínez-Mayorga, K.; Juárez-Gordiano, C.; Castillo, R. *Chem. Med. Chem.* **2007**, *2*, 1141. http://dx.doi.org/10.1002/cmdc.200700054
21. Gupta, A. K.; Plott, T. *Int. J. Dermatol.* **2004**, *43*, 3. http://dx.doi.org/10.1111/j.1461-1244.2004.02380.x
22. Collins, I.; Moyes, C.; Davey, W.; Rowley, M.; Bromidge, F.; Quirk, K.; Atack, J.; McKernan, R.; Thompson, S. A.; Wafford, K.; Dawson, G.; Pike, A.; Sohal, B.; Tsou, N.; Bull, R.; Castro, J. *J. Med. Chem.* **2002**, *45*, 1887. http://dx.doi.org/10.1021/jm0110789
23. Sollogoub, M.; Fox, K. R.; Powers, V. E. C.; Brown, T. *Tetrahedron Lett.* **2002**, *43*, 3121. http://dx.doi.org/10.1016/S0040-4039(02)00481-1
24. Seidel, A.; Brunner, S.; Seidel, P.; Fritz, G. I.; Herbarth, O. *British J. Cancer* **2006**, *94*, 1726.
25. Sun, Z.; Ahmed, S.; McLaughlin, L. W. *J. Org. Chem.* **2006**, *71*, 2922. http://dx.doi.org/10.1021/jo060066y
26. Yang, Z.; Hutter, D.; Sheng, P.; Sismour, A. M.; Benner, S. A. *Nucleic Acids Res.* **2006**, *34*, 6095. http://dx.doi.org/10.1093/nar/gkl633
27. Rajeswaran, M.; Srikrishnan, T. *Nucleosides, Nucleotides Nucleic Acids* **2008**, *27*, 1113. http://dx.doi.org/10.1080/15257770802341319
28. Abdel-Wahab, B. F.; Khidre, R. E.; Awad, G. E. A. *J. Heterocycl.Chem*. **2016**, DOI 10.1002/jhet.2610. http://dx.doi.org/10.1002/jhet.2610
29. Abdel-Wahab, B. F.; Khidre, R. E.; Farahat, A. A.; El-Ahl, A.-A. S. *ARKIVOC* **2012**, *(i)*, 211. http://dx.doi.org/10.3998/ark.5550190.0013.107
30. Abdou, W. M.; Kamel, A. A.; Khidre, R. E.; Geronikaki, A.; Ekonomopoulou, M. T. *Chem. Biol. Drug. Des.* **2012**, *79*, 719. http://dx.doi.org/10.1111/j.1747-0285.2012.01327.x
31. Abdou, W. M.; Shaddy, A. A.; Khidre, R. E.; Awad, G. E. A. *J. Heterocycl. Chem.* **2016**, *53*, 525. http://dx.doi.org/10.1002/jhet.2306
32. Ibrahim, D. A.; Lasheen, D. S.; Zaky, M. Y.; Ibrahim, A. W.; Vullo, D.; Ceruso, M.; Supuran, C. T.; Abou El Ella, D. A. *Bioorg. Med. Chem.* **2015**, *23*, 4989. http://dx.doi.org/10.1016/j.bmc.2015.05.019
33. Ibrahim, D. A.; Abou El Ella, D. A.; El-Motwally, A. M.; Aly, R. M. *Eur. J. Med. Chem.* **2015**, *102*, 115.

http://dx.doi.org/10.1016/j.ejmech.2015.07.030
34. Khidre, R. E.; Abu-Hashem, A. A.; El-Shazly, M. *Eur. J. Med. Chem.* **2011**, *46*, 5057. http://dx.doi.org/10.1016/j.ejmech.2011.08.018
35. Ried, W.; Meyer, A. DE Patent 1189994, **1965**.
36. Traven, V. F.; Ivanov, I. V.; Lebedev, V. S.; Milevskii, B. G.; Chibisova, T. A.; Solov'eva, N. P.; Polshakov, V. I.; Kazheva, O. N.; Alexandrov, G. G.; Dyachenko, O. A. *Mendeleev Commun.* **2009**, *19*, 214. http://dx.doi.org/10.1016/j.mencom.2009.07.014
37. Ried, W.; Schleimer, B. *Justus Liebigs Ann. Chem.* **1959**, *626*, 106. http://dx.doi.org/10.1002/jlac.19596260112

