Synthesis of Some Novel Heteroannulated Pyrano[3,2-*c*]quinoline-2,5(6*H*)-diones

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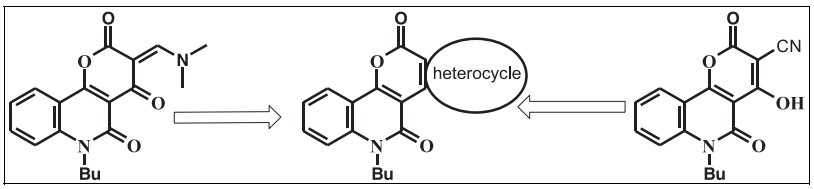

6-Butyl-3-((dimethylamino)methylene)pyrano[3,2-*c*]quinolinone and 6-butyl pyrano[3,2-*c*]quinolone-3-carbonitrile were efficiently synthesized in good yield. These two new precursors were used to obtain some novel heteroannulated pyrano[3,2-*c*]quinolone derivatives from heterocyclization reactions with various binucleophiles. These heteroannulation reactions afforded novel heterocyclic systems fused to the pyranoquinolinone at face *c*, such as pyrazole, pyrimidine, pyridine, and pyrazolopyranone.

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INTRODUCTION

Pyrano[3,2-*c*]quinolinones consider great synthons for many quinolinone derivatives [1–3]. Moreover, they exist in naturally occurring alkaloids [4–6], which are known to display different biological activities [7,8]. Heteroannulated pyranoquinolinones exhibit many important medicinal properties such as antibacterial [9], anticoagulant [10], antitumor [11], and antihypertensive agents [12]. Despite the widespread of published work on the synthesis of these types of compounds with various substituents [13–19], there is a scarcity of literature reports on the preparation of heteroannulated pyrano[3,2-*c*] quinolone derivatives. Moreover, the combination of a pyrazole, pyridine or pyrimidine nucleus with the pyran or quinolinone moiety in one molecular framework is reported to confer biological activity [20–25]. In continuation of our research work directed on the synthesis of heteroannulated pyrano[3,2-*c*]quinolinedione derivatives [26], herein, we disclose the preparation of synthetically valuable 6-butyl-3-((dimethylamino) methylene)pyrano[3,2-*c*]quinolinone **2** and 3-cyanopyrano [3,2-*c*]quinoline **12**. A study of their chemical behavior towards some binucleophiles was investigated. A new series of pyranoquinolinones incorporating a pyrazole, pyrimidine, pyridine, or pyrazolopyranone ring at face *c* was obtained with the hope that these compounds turn out to be biologically active.

RESULTS AND DISCUSSION

A reaction of *N*-butylaniline with two equivalents of diethyl malonate, under solvent-free conditions gave 4-hydroxypyrano[3,2-*c*]quinoline-2,5(6*H*)-dione (**1**) (Fig. 1) [27]. The desired 3-((dimethylamino)methylene) pyrano[3,2-*c*]quinolinone derivative **2** was prepared in good yield *via* thermal condensation of pyranoquinolinone **1** with dimethylformamide dimethylacetal (DMF-DMA). The structure of enamine **2** was confirmed on the basis of ^{1}H NMR spectral data that displays a singlet signal due to the olefinic proton at 8.16 ppm. Moreover, the ^{1}H NMR spectrum reveals two different *N*-methyl groups, one at 3.05 ppm and the other at 3.14 ppm, attributed to Me_2N group. These two methyl groups are observed at 35.25 and 38.36 ppm in the ^{13}C NMR spectrum. In addition, the mass spectrum of compound **2** displays a molecular ion peak at *m*/*z* 340 that is consistent with the formula weight (340.38).

The structure of enamine **2** contains several electron-deficient centers, and it is expected to be quite reactive towards nucleophilic reagents. Therefore, the reaction of enamine **2** with 1,2-binucleophiles such as, hydrazine hydrate and phenylhydrazine in ethanol at room temperature was studied. It is thought that the reaction takes place initially *via* Michael addition to the olefinic carbon of compound **2** followed by elimination of dimethylamine, leading to products **3a**,**b** that were present as interconverting hydrazine and hydrazone tautomers (Fig. 2). The ^{1}H NMR spectra of products **3a**,**b** suggest that they exist predominantly as the hydrazone forms in deuterodimethyl sulfoxide solution. The ^{1}H NMR spectrum of compound **3a** shows two deuterium-exchangeable singlet signals at 5.64 ppm characteristic for NH_2 group and 13.38 ppm due to OH group; while the corresponding signals NH and OH of compound **3b** are observed at 9.41 and 12.37 ppm, respectively. The mass spectra of the compounds **3a**,**b** display molecular

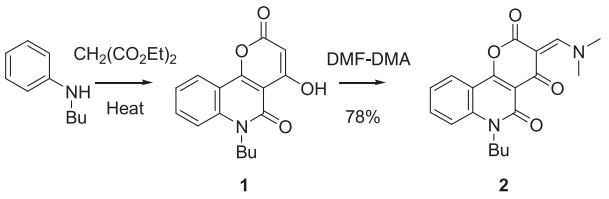

Figure 1. Synthesis of enamine **2**.

ion peaks [M^+] at *m*/*z* 327 and 403, respectively. The hydrazones **3a**,**b** underwent cyclization in acetic acid at reflux to afford the pyrazolopyranoquinolinone derivatives **4a**,**b**, which are obtained directly by refluxing enamine **2** with hydrazine hydrate or phenylhydrazine, respectively, in boiling ethanol (Fig. 2). The ^{1}H NMR spectra of compounds **4a**,**b** exhibit a new characteristic singlet signal at 8.67 and 8.94 ppm, respectively, assigned to pyrazole CH. Also, compound **4a** reveals a deuterium-exchangeable singlet signal at 9.94 ppm ascribed to the NH of the pyrazole ring. The mass spectra of pyrazoles **4a**,**b** display molecular ion peaks [M^+] at *m*/*z* 309 and 385, respectively.

Similarly, treatment of compound **2** with guanidine, cyanoguanidine, and thiourea as 1,3-binucleophiles produced the corresponding pyrimidopyranoquinolinones **5a**–**c** (Fig. 3). The ^{1}H NMR spectra of compounds **5a**–**c** show five aromatic protons, at 7.33–8.76 ppm. In the mass spectra, the molecular ion peaks [M^+] of these compounds appear at *m*/*z* 336, 361, and 353, respectively.

Reaction of enamine **2** with malononitrile as *C*-nucleophile was carried out in boiling ethanol containing small amount of anhydrous potassium carbonate giving rise to pyridopyranoquinoline derivative **8** (Fig. 3). The probable products were pyranopyranoquinolinone **7** or pyridopyranoquinolinone **8**. The IR spectrum of the product exhibited absorption bands at 1725, 1676, and 1648 cm^{-1} attributed to the C═O groups of pyrone, pyridine, and quinolone, respectively. The same compound was obtained from the reaction of compound **2** with cyanoacetamide under the same reaction conditions, thus confirming its structure as that of **8**. The proposed pathway for the formation of compound **8** involves initial nucleophilic addition of the active malononitrile methylene group to the enamine carbon of the side chain and subsequent loss of a molecule of dimethylamine to give the corresponding malononitrile intermediate **6**. Intramolecular 6-*exo-dig* cyclization of the intermediate **6**, followed by rearrangement, leads to the final product **8**.

The reactivity of compound **2** towards a variety of cyclic active methylene compounds; various five- and six-membered heterocycles was studied. Consequently, compound **2** was treated with 3-methyl-2-pyrazolin-5-one, in glacial acetic acid containing freshly fused sodium acetate, to produce pyrazolopyranopyranone **9** (Fig. 4). ^{1}H NMR spectrum of compound **9** shows a peak, at 2.07 ppm due to the methyl group of pyrazole ring, and a singlet signal at 9.20 ppm due to the pyran proton. The mass spectrum of compound **9** reveals a molecular ion peak [M^+] at *m*/*z* 375 that is in agreement with its formula weight (375.39). A pentaheterocyclic system, pyrimidopyranopyranone, was obtained by cyclocondensation of enamine **2** with barbituric acid and thiobarbituric acid, under the same conditions affording derivatives **10a** and **10b** of this ring system (Fig. 4). The IR spectra of **10a** and **10b** show the presence of absorption band due to NH bond at 3280–3105 cm^{-1}. ^{1}H NMR spectra show singlet signals due to the pyran CH that appears at 8.95 ppm for compound **10a** and 8.88 ppm for compound **10b**. In addition, there is a deuterium-exchangeable singlet signal at 13.38 ppm (NH) for compound **10a** and 13.53 ppm (NH) for compound

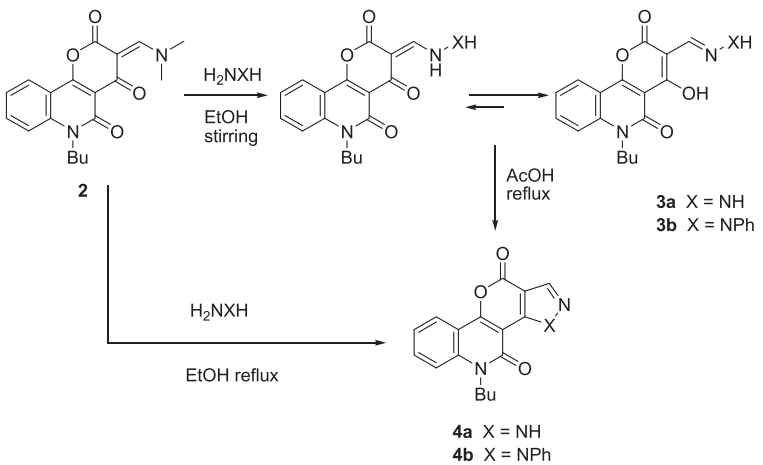

Figure 2. Reaction of enamine **2** with some hydrazines.

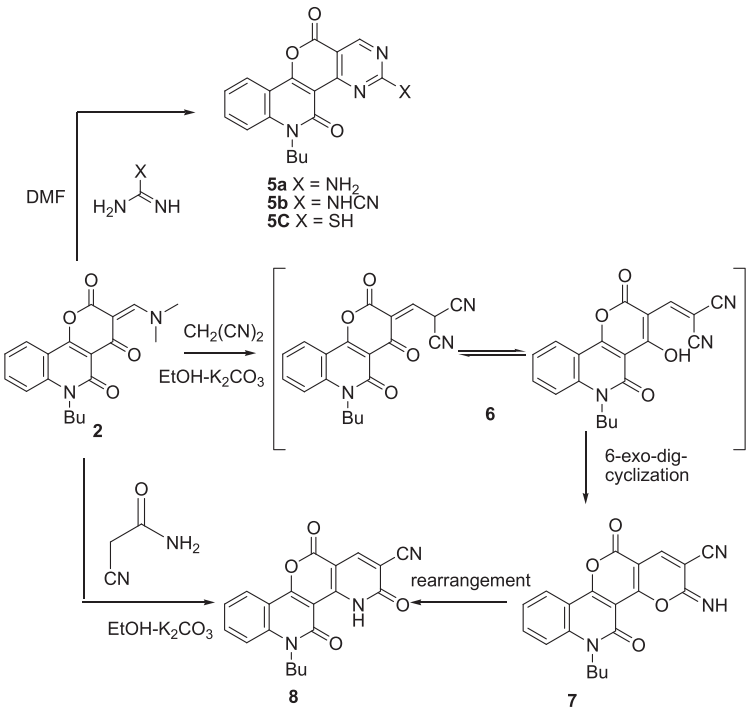

Figure 3. Synthesis of pyrimidopyranoquinolinones **5a**–**c** and pyridopyranoquinoline **8**.

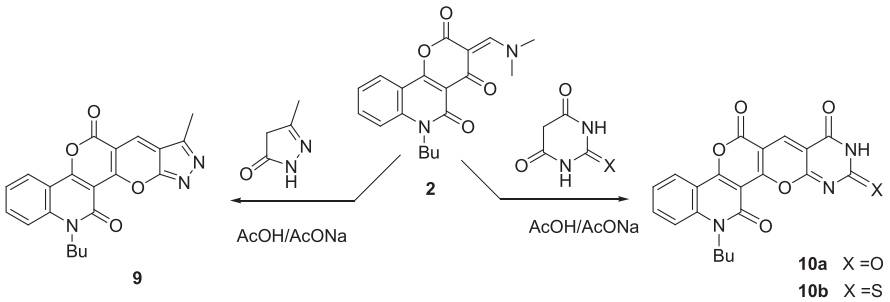

Figure 4. Reaction of compound **2** with some cyclic active methylene compounds.

10b. The mass spectra of compounds **10a**,**b** reveal the correct molecular ion peaks [M^+] at *m*/*z* 405 and 421, respectively.

Continuing the synthesis of new heteoannulated pyrano[3,2-*c*]quinolone derivatives, we planned to prepare the carbonitrile **12** as a new precursor for further functionalized heteroannulated pyranoquinolone derivatives. To approach this target, the reaction of compound **2** with hydroxylamine hydrochloride in boiling ethanol was carried out yielding the oxime **11**. This compound underwent dehydration in boiling glacial acetic acid to give the desired carbonitrile **12** (Fig. 5). Its IR spectrum exhibits the characteristic vibrational absorption band at 2200 cm^{-1} due to (C≡N). Furthermore, the ^1H NMR spectrum of compound **12** displays a deuterium-exchangeable singlet signal at 12.38 ppm assignable to OH. The structure of compound **12** was further confirmed from its mass spectrum, which revealed a molecular ion peak at *m*/*z* 310.

Heterocyclization at face *c* of the pyran moiety can take place when compound **12** is treated with binucleophiles. Because the active cyano group at position-3 is susceptible to nucleophilic addition and OH function at position-4 participates in heterocyclization through nucleophilic substitution. Hence, compound **12** was reacted with hydrazine hydrate, phenyl hydrazine, and hydroxylamine hydrochloride in boiling glacial acetic acid to give pyrazolopyranones **13a**,**b** and isoxazolopyranone **13c**, respectively (Fig. 6). Evidence for the formation of the pyrazole derivatives **13a**–**c** is from their IR spectra where there is an absence of the OH absorption band and the appearance of two characteristic absorption bands at 3526–3368 cm^{-1} that corresponds to the amine functionality. Furthermore, the ^1H NMR

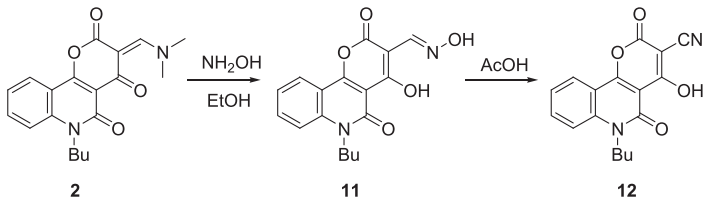

Figure 5. Preparation of carbonitrile **12**.

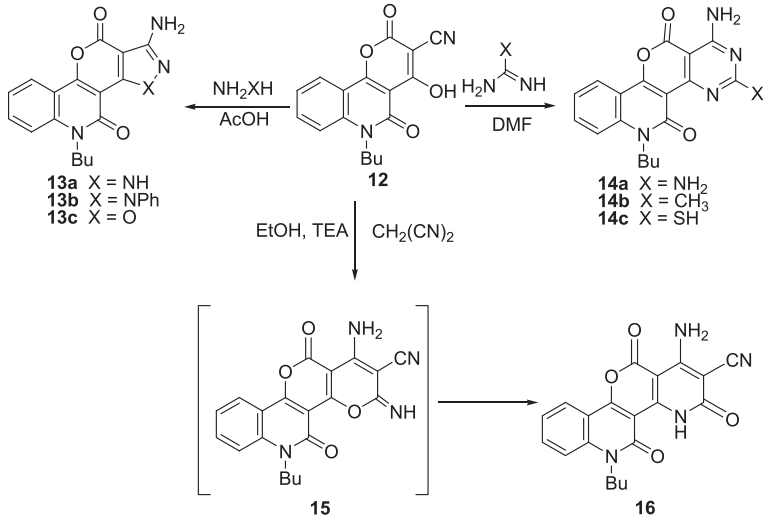

Figure 6. Reaction of carbonitrile **12** with some 1,2-, 1,3-binucleophiles, and malononitrile.

spectra display a deuterium-exchangeable singlet signal in the range of 6.98–7.20 ppm assigned to NH_2. Mass spectra show the correct molecular ion peaks at *m*/*z* 324, 400, and 325, respectively.

The carbonitrile **12**, as a bifunctional electrophile, represents a good building unit for the synthesis of a series of pyrimidopyrano[3,2-*c*]quinolinones, *via* its cyclocondensation reactions with a variety of 1,3-bifiunctional nucleophiles. Thus, condensation of carbonitrile **12** with guanidine hydrochloride, acetamidine, or thiourea in boiling DMF produced the suggested pyrimidine derivatives **14a**–**c** (Fig. 6). The ^{1}H NMR spectra of these compounds show an exchangeable signal at 6.97–7.37 ppm characteristic for NH_2 protons. Further evidence is from their mass spectra that reveal the correct molecular ion peaks [M^+] at *m*/*z* 351, 350, and 368 respectively. The elemental analyses of the products are in agreement with their proposed formulae. The predominance of the amino tautomer of compounds **14a**–**c** (Fig. 6) is expected because there is a literature report that supports that the amino form is more predominant than the imino form [28].

Reaction of the carbonitriles with malononitrile was previously studied [29,30]. Thus, compound **12** was treated with malononitrile, in boiling ethanol containing few drops of triethylamine, affording pyridopyranone derivative **16** *via* the non-isolable intermediate **15** (Fig. 6). The IR spectrum exhibited absorption bands at 3473 and 3335 cm^{-1} due to amino group and 2189 cm^{-1} attributed to the nitrile function. Three carbonyl groups are observed, at 1752 cm^{-1} (α-pyrone), 1669 cm^{-1} (pyridone), and 1636 cm^{-1} (quinolone), respectively. The ^{1}H NMR spectrum of compound **16** showed exchangeable singlet signals attributed to NH_2 and NH proton at 7.72 and 13.15 ppm, respectively. In the ^{13}C NMR spectrum, there are three characteristic downfield signals at 170.61, 164.49, and 158.89 ppm that attributed the carbonyl carbon atoms of α-pyrone, pyridine, and quinolone, respectively. Also, the structure of compound **16** was further confirmed from its mass spectrum that revealed the molecular ion peak at *m*/*z* 376 that agreed well with its suggested molecular formula.

Pyrano[3,2-*c*]quinolinones undergo ring opening at C-2 and ring reclosure at C-4 when reacted with binucleophiles [2,31]. However, we introduce the more highly reactive enamine or nitrile function at the 3-position of pyranoquinolinone, use mild condition, and avoid using a strong basic media, in order to direct the binucleophiles to heterocyclization at face [c] with retention of 2-pyranone nucleus. Notable in the IR

spectra of the desired compounds is the presence of a band at 1720–1750 cm^{-1} due to the carbonyl group of the 2-pyranone moiety.

CONCLUSION

In the present work, the novel enamine **2** and carbonitrile **12** were efficiently synthesized and utilized as good precursors to obtain a series of novel annulated heterocyclic systems containing the pyrano[3,2-*c*]quinolinedione skeleton.

EXPERIMENTAL

Melting points were determined on a digital Stuart SMP3 apparatus. IR spectra were measured on a Perkin-Elmer 293 spectrophotometer (cm^{-1}), using KBr disks. ^1H NMR (400 MHz) and ^{13}C NMR (101 MHz) measurements were performed using a Mercury-400BB, and Varian-400 spectrometers, and chemical shifts were expressed in δ (ppm) relative to tetramethylsilane (in $CDCl_3$ or DMSO-d_6 as solvent) as the internal standard. Mass spectra were obtained using the GC-2010 Shimadzu gas chromatography mass spectrometer (70 eV). Elemental microanalyses were performed on a Perkin–Elmer CHN-2400II analyzer at the Chemical War department, Ministry of Defense, Cairo, Egypt. Thin-layer chromatography (TLC) was carried out on aluminum sheets covered with silica gel 60 F_{254}, 0.2 mm layer (Merck). Column flash chromatography was performed on Fluka analytical silica gel 60 0.063–0.2 mm (70–230 mesh ASTM) using UV light (254 and 366 nm) for detection.

6-Butyl-3H-pyrano[3,2-c]quinoline-2,4,5(6H)-trione (1). This compound was prepared according to the published method [27], mp 227–229°C.

6-Butyl-3-((dimethylamino)methylene)-3H-pyrano[3,2-c] quinoline-2,4,5(6H)-trione (2). A mixture of pyranoquinolinone **1** (2.85 g, 10 mmol) and dimethyl formamide dimethylacetal (4 mL, 30 mmol) was refluxed for 4 h under free-solvent condition at 100°C. The course of the reaction was monitored by TLC until the starting material had completely disappeared. The crude product was filtered off, purified by flash chromatography and compound **2** was eluted with n-hexane: EtOAc (4:6). After evaporation of the solvent, compound **2** was obtained as yellow crystals (2.66 g, 78%) mp 190–192°C. TLC (silica gel, n-hexane: EtOAc (4:6)): R_f 0.79. IR (KBr, cm^{-1}) ν_{max}: 3042 (CH_{arom}), 2971, 2936, 2860 (CH_{aliph}), 1720 ($C{=}O_{\alpha\text{-pyrone}}$), 1674 ($C{=}O_{\gamma\text{-pyrone}}$), 1627 ($C{=}O_{quinolone}$), 1592 (C=C). ^1H NMR (DMSO-d_6) δ_H: 0.91 (t, 3H, *J* = 8.0 Hz, CH_2CH_3), 1.39–1.41 (m, 2H, CH_2CH_3), 1.57–1.62 (m, 2H, CH_2CH_2), 3.05 (s, 3H, NCH_3), 3.14 (s, 3H, NCH_3), 4.19 (t, 2H, *J* = 8.0 Hz, NCH_2), 7.34 (t, 1H, *J* = 8.4 Hz, H-9), 7.60 (d, 1H, *J* = 8.4 Hz, H-7), 7.70 (t, 1H, *J* = 8.2 Hz, H-8), 8.04 (d, 1H, *J* = 8.4 Hz, H-10), 8.16 (s, 1H, $CH_{olefinic}$). ^{13}C NMR (125 MHz, DMSO-d_6) δ_C: 13.81 (CH_3), 20.16 (CH_2), 29.52 (CH_2), 35.25 (NCH_3), 38.36 (NCH_3), 42.60 (NCH_2), 102.53, 107.34, 113.04, 114.93, 123.02, 124.24, 126.33, 133.89, 139.65, 141.10, 156.84, 158.89, 164.51. MS: *m*/*z* (relative intensity): 341 [M^++ 1; 6], 340 [M^+; 25], 312 (6), 311 (7), 297 (10), 296 (25), 284 (6), 283 (26), 268 (4), 254 (5), 253 (8), 241 (15), 240 (18), 215 (10), 213 (7), 212 (9), 201 (15), 187 (14), 172 (4), 161 (11), 159 (3), 158 (3), 133 (13), 132 (100), 119 (22), 104 (17), 77 (56). *Anal*. Calcd for $C_{19}H_{20}N_2O_4$ (340.38): C, 67.05; H, 5.92; N, 8.23. Found: C, 67.08; H, 5.89; N, 8.33%.

General procedure for formation of 3-(hydrazonomethylene) pyrano quinolinediones (3a,b). A mixture of enamine **2** (3.40 g, 10 mmol) and hydrazine hydrate (0.50 mL, 10 mmol), or phenylhydrazine (1.1 mL, 10 mmol), in ethanol (25 mL) was stirred at room temperature for 8 h. After partial evaporation of the solvent, the solid deposited after cooling was isolated by filtration, air dried, and crystallized from the proper solvent to give compounds **3a**,**b**.

6-Butyl-4-hydroxy-3-(hydrazonomethylene)pyrano[3,2-c] quinoline-2,5(6H)-dione (3a). Crystallized from EtOH to give orange crystals, (2.65 g, 81%), mp 254–255°C. IR (KBr, cm^{-1}) ν_{max}: 3526, 3357 3234 (NH_2 and OH), 3049 (CH_{arom}), 2953, 2942, 2860 (CH_{aliph}), 1709 ($C{=}O_{\alpha\text{-pyrone}}$), 1679 ($C{=}O_{\gamma\text{-pyrone}}$), 1636 ($C{=}O_{quinolone}$), 1574 (C=C). ^1H NMR ($CDCl_3$, δ) δ_H: 0.97 (t, 3H, *J* = 8.0 Hz, CH_2CH_3), 1.45–1.50 (m, 2H, CH_2CH_3), 1.71–1.75 (m, 2H, CH_2CH_2), 4.29 (t, 2H, *J* = 8.1 Hz, NCH_2), 5.64 (s, 2H, NH_2), 7.33 (t, 1H, *J* = 8.0 Hz, H-9), 7.46 (d, 1H, *J* = 8.0 Hz, H-7), 7.70 (t, 1H, *J* = 8.0 Hz, H-8), 8.17 (d, 1H, *J* = 8.0 Hz, H-10), 8.94 (s, 1H, $CH_{enamine}$), 13.38 (s, 1H, OH). ^{13}C NMR (125 MHz, DMSO-d_6) δ_C: 14.12 (CH_3), 19.93 (CH_2), 29.91 (CH_2), 42.07 (NCH_2), 101.69, 114.0 0, 114.88, 116.37, 122.70, 124.37, 132.20, 136.08, 137.99, 145.92, 148.44, 158.98, 162.80. MS: *m*/*z* (relative intensity): 327 [M^+; 3], 326 [M^+– 1; 1], 310 (1), 309 (3), 298 (1), 285 (4), 284 (2), 270 (1), 254 (1), 253 (5), 240 (3), 239 (2), 215 (7), 201 (8), 187 (5), 161 (35), 132 (100), 119 (32), 105 (19), 104 (14), 91 (10), 77 (53). *Anal*. Calcd for $C_{17}H_{17}N_3O_4$ (327.34): C, 62.38; H, 5.23; N, 12.84. Found: C, 62.40; H, 5.28; N, 12.81%.

6-Butyl-4-hydroxy-3-(N′-phenylhydrazonomethylene)pyrano [3,2-c]quinoline-2,5(6H)-dione (3b). Crystallized from EtOH as yellow crystals, (3.12 g, 77%), mp 242–243°C. IR (KBr, cm^{-1}) ν_{max}: 3266 (NH), 3049 (CH_{arom}), 2954, 2930, 2855 (CH_{aliph}), 1752 ($C{=}O_{\alpha\text{-pyrone}}$), 1677

(C═$O_{\gamma\text{-pyrone}}$), 1639 (C═$O_{quinolone}$), 1615 (C═N), 1573 (C═C). ^{1}H NMR (DMSO-d_6) δ_H: 1.02 (t, 3H, J = 8.0 Hz, CH_2CH_3), 1.52–1.55 (m, 2H, CH_2CH_3), 1.77–1.83 (m, 2H, CH_2CH_2), 4.35 (t, 2H, J = 8.1 Hz, NCH_2), 7.12–7.16 (m, 2H, Ar─H), 7.25 (s, 1H, $CH_{enamine}$), 7.48–7.56 (m, 3H, Ar─H), 7.76 (t, 1H, J = 8.2 Hz, Ar─H), 7.94–8.23 (m, 2H, Ar─H), 8.33 (d, 1H, J = 7.2 Hz, Ar─H), 9.41 (s, 1H, NH), 12.37 (s, 1H, OH). ^{13}C NMR (125 MHz, DMSO-d_6) δ_C: 13.77 (CH_3), 20.18 (CH_2), 29.58 (CH_2), 42.50 (NCH_2), 100.57, 113.70, 113.84, 115.11, 115.61, 115.83, 124.12, 124.81, 130.73, 133.62, 133.77, 137.89, 156.02, 157.82, 160.25, 161.89, 163.17, 163.39, 165.89. MS: m/z (relative intensity): 404 [M^++ 1; 10], 403 [M^+; 38], 402 [M^+− 1; 1], 347 (1), 310 (1), 297 (23), 296 (100), 285 (1), 268 (3), 254 (2), 241 (41), 240 (30), 228 (1), 226 (1), 212 (18), 185 (5), 158 (2), 156 (37), 146 (9), 141 (11), 140 (10), 132 (19), 118 (1), 114 (7), 104 (5), 92 (10), 77 (69). *Anal*. Calcd for $C_{23}H_{21}N_3O_4$ (403.44): C, 68.47; H, 5.25; N, 10.42. Found: C, 68.50; H, 5.21; N, 10.40%.

General procedures for preparation of pyrazolo[3′,4′:4,5] pyrano[3,2-*c*]quinolineones (4a,b). *Procedure a*: A mixture of enamine **2** (3.40 g, 10 mmol) and hydrazine hydrate (0.50 mL, 10 mmol), or phenylhydrazine (1.1 mL, 10 mmol), in absolute ethanol (25 mL) was refluxed for 8 h. The solid deposited during heating was separated by filtration, air dried, and crystallized from the proper solvent to give compounds **4a** and **4b**, respectively.

5-Butyl-3H-pyrazolo[3′,4′:4,5]pyrano[3,2-c]quinoline-4,11 (5H)-dione (4a). Crystallized from DMF/H_2O afforded compound **4a** as brown crystals (2.45 g, 79%), mp 200–201°C. IR (KBr, cm^{-1}) ν_{max}: 3292 (NH), 3035 (CH_{arom}), 2958, 2932, 2876 (CH_{aliph}), 1728 (C═$O_{\alpha\text{-pyrone}}$), 1679 (C═$O_{quinoline}$), 1613 (C═N), 1576 (C═C). ^{1}H NMR (DMSO-d_6) δ_H: 0.89 (t, 3H, J = 8.1 Hz, CH_2CH_3), 1.35–1.40 (m, 2H, CH_2CH_3), 1.46–1.52 (m, 2H, CH_2CH_2), 4.16 (t, 2H, J = 8.1 Hz, NCH_2), 7.34 (t, 1H, J = 8.0 Hz, H-8), 7.57 (d, 1H, J = 8.0 Hz, H-6), 7.73 (t, 1H, J = 8.0 Hz, H-7), 8.07 (d, 1H, J = 8.0 Hz, H-9), 8.67 (s, 1H, $CH_{pyrazole}$), 9.94 (s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6) δ_C: 14.10 (CH_3), 19.90 (CH_2), 29.62 (CH_2), 42.24 (NCH_2), 99.70, 102.46, 113.51, 116.6, 123.86, 124.66, 134.44, 137.90, 139.27, 157.21, 160.08, 163.14, 163.83. MS: m/z (relative intensity): 309 [M^+; 2], 308 [M^+− 1; 3], 295 (1), 268 (14), 253 (4), 240 (43), 239 (12), 228 (13), 226 (6), 215 (56), 201 (94), 188 (14), 187 (34), 172 (19), 160 (3), 159 (19), 132 (100), 119 (30), 104 (22), 105 (16), 90 (15), 77 (64). *Anal*. Calcd for $C_{17}H_{15}N_3O_3$ (309.33): C, 66.01; H, 4.89; N, 13.58. Found: C, 66.00; H, 4.91; N, 13.60%.

5-Butyl-3-phenyl-3H-pyrazolo[3′,4′:4,5]pyrano[3,2-c]quinoline-4,11(5H)-dione (4b). Crystallized from DMF affording compound **4b** as yellow crystals, (2.96 g, 77%), mp 212–213°C. IR (KBr, cm^{-1}) ν_{max}: 3082 (CH_{arom}), 2957, 2929, 2868 (CH_{aliph}), 1713 (C═$O_{\alpha\text{-pyrone}}$), 1673 (C═$O_{quinolone}$), 1614 (C═N), 1570 (C═C). ^{1}H NMR (DMSO-d_6) δ_H: 0.90 (t, 3H, J = 7.6 Hz, CH_2CH_3), 1.40–1.45 (m, 2H, CH_2CH_3), 1.61–1.65 (m, 2H, CH_2CH_2), 4.31 (t, 2H, J = 8.0 Hz, NCH_2), 7.11 (t, 1H, J = 8.2 Hz, Ar─H), 7.29 (t, 1H, J = 8.2 Hz, Ar─H), 7.42 (t, 1H, J = 7.4 Hz, Ar─H), 7.50 (d, 1H, J = 8.4 Hz, Ar─H), 7.72–7.78 (m, 2H, Ar─H), 7.86 (t, 1H, J = 8.2 Hz, Ar─H), 8.05 (d, 1H, J = 8.2 Hz, Ar─H), 8.14 (d, 1H, J = 8.1 Hz, Ar─H), 8.94 (s, 1H, $CH_{pyrazole}$). ^{13}C NMR (100.62 MHz, DMSO-d_6) δ_C: 14.01 (CH_3), 20.06 (CH_2), 29.71 (CH_2), 42.34 (NCH_2), 99.86, 102.64, 113.69, 115.16, 116.62, 118.70, 122.36, 123.03, 123.91, 124.62, 134.38, 134.80, 138.05, 157.32, 158.40, 160.08, 163.28, 163.41, 163.85. MS: m/z (relative intensity): 385 [M^+; 55], 384 [M^+− 1; 88], 370 (63), 343 (65), 328 (75), 293 (100), 215 (63), 188 (60), 160 (55), 105 (58), 104 (97). *Anal*. Calcd for $C_{23}H_{19}N_3O_3$ (385.43): C, 71.68; H, 4.97; N, 10.90. Found: C, 71.70; H, 4.99; N, 10.30%.

Procedure b: A solution of hydrazone **3a** (3.27 g, 10 mmol) or **3b** (4.03 g, 10 mmol) in glacial acetic acid (50 mL) was heated under reflux for 6 h. The reaction mixture was concentrated in vacuum and the obtained solid was filtered and recrystallized from the proper solvent to give compounds **4a** (2.51 g, 81%) and **4b** (3.03 g, 79%).

General procedure for formation of pyrimido[4′,5′:4,5] pyrano[3,2-*c*]quinolinones (5a–c). A mixture of enamine **2** (3.40 g, 10 mmol) and 1,3-binucleophiles, *viz.* guanidine hydrochloride (0.95 g, 10 mmol), cyanoguanidine (0.84 gm, 10 mmol), thiourea (0.76 gm, 10 mmol) in DMF (50 mL) was refluxed for 8 h. The solid precipitated during heating was collected by filtration, air dried, and crystallized from the proper solvent to give compounds **5a**, **5b**, and **5c**, respectively.

3-Amino-6-butyl-4H-pyrimido[4′,5′:4,5]pyrano[3,2-c]quinoline-5,12(6H)-dione (5a). Was crystallized from AcOH to afford compound **5a** as brown crystals, (2.92 g, 87%), mp 176–177°C. IR (KBr, cm^{-1}) ν_{max}: 3483, 3395 (NH_2), 2955, 2929, 2867 (CH_{aliph}), 1727 (C═$O_{\alpha\text{-pyrone}}$), 1669 (C═$O_{quinolone}$), 1621 (C═N), 1585 (C═C). ^{1}H NMR (DMSO-d_6) δ_H: 0.91 (t, 3H, J = 8.0 Hz, CH_2CH_3), 1.41–1.46 (m, 2H, CH_2CH_3), 1.68–1.73 (m, 2H, CH_2CH_2), 4.29 (t, 2H, J = 8.0 Hz, NCH_2), 7.13 (s, 2H, NH_2), 7.52 (t, 1H, J = 8.2 Hz, H-9), 7.66–7.87 (m, 2H, H-7 and H-8), 8.17 (d, 1H, J = 8.1 Hz, H-10), 8.53 (s, 1H, $H_{pyrimidine}$). ^{13}C NMR (125 MHz, DMSO-d_6) δ_C: 14.02 (CH_3), 19.92 (CH_2), 29.71 (CH_2), 42.34 (NCH_2), 99.87, 102.63, 113.71, 113.84, 116.65, 123.94, 124.63, 134.39, 138.08, 151.26, 157.34, 160.08, 163.30, 163.84. MS: m/z (relative intensity): 337 [M^++ 1; 7], 336 [M^+; 50], 308 (22), 273 (13), 265 (17), 217 (100), 195 (41),

178 (28), 149 (25), 109 (13), 105 (25), 71 (27). *Anal*. Calcd for $C_{18}H_{16}N_4O_3$ (336.35): C, 64.28; H, 4.79; N, 16.66. Found: C, 64.08; H, 4.71; N, 16.55%.

N-(6-Butyl-5,12-dioxo-5H-pyrimido[4′,5′:4,5]pyrano[3,2-c] quinolin-3-yl)cyanamide (5b). Crystallized from AcOH to give compound **5b** as brown crystals, (3.00 g, 83%), mp 186–187°C. IR (KBr, cm^{-1}) ν_{max}: 3304 (NH), 3053 (CH_{arom}), 2959, 2926, 2878 (CH_{aliph}), 2008 (CN), 1715 ($C{=}O_{\alpha\text{-pyrone}}$), 1677 ($C{=}O_{quinolone}$), 1611(C═N), 1573 (C═C). ^{1}H NMR (DMSO-d_6) δ_H: 0.94 (t, 3H, J = 8.0 Hz, CH_2CH_3), 1.42–1.47 (m, 2H, CH_2CH_3), 1.67–1.73 (m, 2H, CH_2CH_2), 4.33 (t, 2H, J = 7.6 Hz, NCH_2), 6.48 (s, 1H, NH), 7.33 (t, 1H, J = 8.2 Hz, H-9), 7.53 (d, 1H, J = 8.2 Hz, H-7), 7.82 (t, 1H, J = 8.2 Hz, H-8), 8.14 (d, 1H, J = 8.2 Hz, H-10), 8.76 (s, 1H, $CH_{pyrimidine}$). ^{13}C NMR (101 MHz, DMSO-d_6) δ_C: 14.10 (CH_3), 19.90 (CH_2), 29.82 (CH_2), 42.24 (NCH_2), 88.62 (C≡N), 99.70, 102.46, 112.78, 113.51, 116.65, 123.86, 124.66, 134.44, 137.90, 157.21, 160.08, 163.14, 163.83, 173.18. MS: *m*/*z* (relative intensity): 361 [M^+; 3], 336 (12), 320 (6), 319 (3), 294 (7), 280 (17), 268 (21), 253 (18), 240 (64), 228 (14), 215 (58), 201 (95), 200 (8), 187 (10), 184 (9), 172 (9), 158 (12), 145 (15), 132 (100), 104 (45), 90 (51), 76 (41). *Anal*. Calcd for $C_{19}H_{15}N_5O_3$ (361.36): C, 63.15; H, 4.18; N, 19.38. Found: C, 63.20; H, 4.16; N, 19.33%.

6-Butyl-3-thioxo-5H-pyrimido[4′,5′:4,5]pyrano[3,2-c]quinoline-5,12(6H)-dione (5c). Formed brown crystals (2.90 g, 82%), mp 211–212°C, and crystallized from DMF. IR (KBr, cm^{-1}) ν_{max}: 3166 (NH), 3080 (CH_{arom}), 2954, 2928, 2866 (CH_{aliph}), 1724 ($C{=}O_{\alpha\text{-pyrone}}$), 1659 ($C{=}O_{quinolone}$), 1623 (C═N), 1600 (C═C). ^{1}H NMR (DMSO-d_6) δ_H: 0.99 (t, 3H, J = 8.1 Hz, CH_2CH_3), 1.47–1.54 (m, 2H, CH_2CH_3), 1.72–1.76 (m, 2H, CH_2CH_2), 4.30 (t, 2H, J = 7.8 Hz, NCH_2), 7.39–7.41 (m, 2H, H-9 and H-7), 7.69 (t, 1H, J = 8.2 Hz, H-8), 8.24 (d, 1H, J = 8.1 Hz, H-10), 8.35 (s, 1H, $CH_{pyrimidine}$), 13.36 (s, 1H, NH). ^{13}C NMR (101 MHz, DMSO-d_6) δ_C: 14.13 (CH_3), 21.21 (CH_2), 29.59 (CH_2), 41.90 (NCH_2), 100.17, 112.93, 116.15, 123.60, 123.83, 125.89, 128.60, 130.33, 134.16, 138.42, 145.54, 156.36, 163.33, 165.98. MS: *m*/*z* (relative intensity): 354 [M^++ 1; 4], 353 [M^+; 8], 310 (25), 270 (28), 267 (11), 239 (27), 170 (48), 160 (12), 132 (100), 105 (14), 77 (95). *Anal*. Calcd for $C_{18}H_{15}N_3O_3S$ (353.40): C, 61.18; H, 4.28; N, 11.89; S, 9.07. Found: C, 61.20; H, 4.23; N, 11.90; S, 9.05%.

6-Butyl-3,5,12-trioxo-3H-pyrido[2′,3′:4,5]pyrano[3,2-c]quinoline-2-carbonitrile (8). *Procedure a*: Enamine **2** (3.40 g, 10 mmol) was heated under reflux for 4 h with malononitrile (0.66 g, 10 mmol) in ethanol containing a small amount of potassium carbonate. The solid deposited was then filtered and air dried. Crystallization from DMF afforded compound **8** as white crystals, (3.00 g, 83%), mp 271–272°C. IR (KBr, cm^{-1}) ν_{max}: 3223 (NH), 3083 (CH_{arom}), 2959, 2932, 2871 (CH_{aliph}), 2211 (C≡N), 1725 ($C{=}O_{pyrone}$), 1676 ($C{=}O_{pyridone}$), 1648 ($C{=}O_{quinoline}$), 1617 (C═N), 1572 (C═C). ^{1}H NMR (DMSO-d_6) δ_H: 0.93 (t, 3H, J = 8.0 Hz, CH_2CH_3), 1.42–1.50 (m, 2H, CH_2CH_3), 1.64–1.67 (m, 2H, CH_2CH_2), 4.33 (t, 2H, J = 8.0 Hz, NCH_2), 7.54 (t, 1H, J = 7.8 Hz, H-9), 7.87–7.92 (m, 2H, H-7, and H-8), 8.16 (d, 1H, J = 7.8 Hz, H-10), 8.77 (s, 1H, $CH_{pyridone}$), 13.50 (s, 1H, NH). MS: *m*/*z* (relative intensity): 362 [M^++ 1; 2], 361 [M^+; 6], 336 (1), 332 (1), 319 (2), 308 (2), 305(4), 282 (2), 277 (7), 268 (6), 240 (25), 226 (4), 215 (33), 201 (51), 188 (11), 187 (16), 172 (13), 160 (2), 159 (16), 145 (44), 132 (92), 119 (36), 117 (35), 115 (11), 104 (33), 91 (14), 90 (23), 77 (100), 76 (26). *Anal*. Calcd for $C_{20}H_{15}N_3O_4$ (361.36): C, 66.48; H, 4.18; N, 11.63. Found: C, 66.50; H, 4.19; N, 11.60%.

Procedure b: A solution of enamine **2** (3.40 g, 10 mmol), in DMF (50 mL), was refluxed for 4 h with cyanoacetamide (0.84 g, 10 mmol). The solid deposited after cooling was collected by filtration and crystallized from DMF giving compound **8** as white crystals, (3.21 g, 89%), mp 273–275°C.

13-Butyl-8-methyl-6H-pyrazolo[4″,3″:5′,6′]pyrano[2′,3′:4,5] pyrano[3,2-c]quinoline-6,12(13H)-dione (9). To a solution of enamine **2** (3.40 g, 10 mmol) in glacial acetic acid containing freshly fused sodium acetate, 3-methyl-2-pyrazolin-5-one (0.98 g, 10 mmol) was added. Then, the reaction mixture was refluxed for 4 h. The crystals deposited were filtered and air dried. Crystallization from DMF afforded compound **9** as yellow crystals, (3.00 g, 80%), mp 193–194°C. IR (KBr, cm^{-1}) ν_{max}: 3072 (CH_{arom}), 2958, 2925, 2869 (CH_{aliph}), 1718 ($C{=}O_{pyrone}$), 1670 ($C{=}O_{quinolinone}$), 1614 (C═N), 1570 (C═C). ^{1}H NMR (DMSO-d_6) δ_H: 0.98 (t, 3H, J = 8.1 Hz, CH_2CH_3), 1.45–1.51 (m, 2H, CH_2CH_3), 1.76–1.79 (m, 2H, CH_2CH_2), 2.07 (s, 3H, CH_3), 4.45 (t, 2H, J = 8.1 Hz, NCH_2), 7.37 (t, 1H, J = 8.0 Hz, H-3), 7.65–7.68 (m, 2H, H-1 and H-2), 8.21 (d, 1H, J = 8.1 Hz, H-4), 9.20 (s, 1H, CH_{pyran}). MS: *m*/*z* (relative intensity): 376 [M^++ 1; 18], 375 [M^+; 69], 360 (1), 319 (2), 284 (4), 283 (9), 268 (2), 241 (3), 240 (2), 239 (3), 217 (15), 216 (100), 201 (3), 189 (17), 188 (36), 187 (9), 172 (5), 161 (13), 158 (3), 133 (8), 132 (26), 120 (41), 119 (15), 105 (11), 104 (14), 77 (61). *Anal*. Calcd for $C_{21}H_{17}N_3O_4$ (375.39): C, 67.19; H, 4.56; N, 11.19. Found: C, 67.22; H, 4.60; N, 11.20%.

General procedure for formation of pyrimido[5″,4″:5′, 6′]pyrano[2′,3′:4,5]pyrano [3,2-*c*]quinolinones (10a,b). Compound **2** (3.40 g, 10 mmol) was heated under reflux with barbituric acid (1.28 g, 10 mmol) or thiobarbituric acid (1.44 g, 10 mmol), in glacial acetic acid containing freshly fused sodium acetate for 4 h. The course of the reaction was monitored by TLC until the starting

material had completely disappeared. The solid obtained after cooling was filtered and crystallized from the proper solvent to give compounds **10a**,**b**.

14-Butyl-6H,8H-pyrimido[5″,4″:5′,6′]pyrano[2′,3′:4,5]pyrano[3,2-c]quinoline-6,8,10,13(14H)-tetraone (10a). This compound obtained as yellow crystals by crystallization from DMF, (3.50 g, 86%), mp 266–267°C. IR (KBr, cm^{-1}) ν_{max}: 3162 (NH), 3072 (CH_{arom}), 2955, 2929, 2860 (CH_{aliph}), 1716 ($C{=}O_{pyrone}$), 1666 ($2C{=}O_{pyrimidone}$), 1644 ($C{=}O_{quinoline}$), 1614 (C=N), 1569 (C=C). ^{1}H NMR ($CDCl_3$) δ_H: 0.98 (t, 3H, J = 8.0 Hz, CH_2CH_3), 1.47–1.52 (m, 2H, CH_2CH_3), 1.70–1.75 (m, 2H, CH_2CH_2), 4.31 (t, 2H, J = 8.0 Hz, NCH_2), 7.33 (t, 1H, J = 8.2 Hz, H-2), 7.57 (d, 1H, J = 8.2 Hz, H-1), 8.07 (t, 1H, J = 8.2 Hz, H-3), 8.23 (d, 1H, J = 8.2 Hz, H-4), 8.95 (s, 1H, CH_{pyran}), 13.38 (s, 1H, NH). MS: m/z (relative intensity): 405 [M^+; 100], 387 (15), 319 (5), 283 (17), 282 (25), 228 (6), 156 (12), 105 (18). *Anal*. Calcd for $C_{21}H_{15}N_3O_6$ (405.37): C, 62.22; H, 3.73; N, 10.37. Found: C, 62.34; H, 3.70; N, 10.31%.

14-Butyl-10-thioxo-6H,8H-pyrimido[5″,4″:5′,6′]pyrano[2′,3′:4,5]pyrano[3,2-c]quinoline-6,8,13(14H)-trione (10b). This compound produced yellow crystals (3.00 g, 71%), mp 174–175°C, and crystallized from DMF. IR (KBr, cm^{-1}) ν_{max}: 3280, 3105 (NH), 3049 (CH_{arom}), 2954, 2864 (CH_{aliph}), 1715 ($C{=}O_{pyrone}$), 1672 ($C{=}O_{pyrimidone}$), 1639 ($C{=}O_{quinoline}$), 1582 (C=C). ^{1}H NMR (DMSO-d_6) δ_H: 1.01 (t, 3H, J = 8.0 Hz, CH_2CH_3), 1.49–1.54 (m, 2H, CH_2CH_3), 1.75–1.81 (m, 2H, CH_2CH_2), 4.33 (t, 2H, J = 8.0 Hz, NCH_2), 7.37–7.80 (m, 2H, H-2 and H-1), 7.96 (t, 1H, J = 8.0 Hz, H-3), 8.20 (d, 1H, J = 8.0 Hz, H-4), 8.88 (s, 1H, H_{pyran}), 13.53 (s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6) δ_C: 13.84 (CH_3), 20.25 (CH_2), 29.68 (CH_2), 43.48 (NCH_2), 104.35, 114.15, 114.36, 116.21, 118.13, 122.29, 122.56, 124.54, 125.36, 132.35, 138.78, 148.78, 165.27, 166.47, 183.70, 188.13, 191.19. MS: m/z (relative intensity): 422 [M^++ 1; 3], 421 [M^+; 9], 405 (14), 377 (6), 365 (3), 320 (11), 285 (7), 268 (12), 267 (69), 257 (100), 216 (11), 212 (58), 202 (21), 188 (4), 187 (12), 186 (24), 172 (19), 161 (9), 118 (8), 104 (10), 91(24), 77 (43). *Anal*. Calcd for $C_{21}H_{15}N_3O_5S$ (421.43): C, 59.85; H, 3.59; N, 9.97; S, 7.61. Found: C, 59.86; H, 3.60; N, 9.99; S, 7.55%.

6-Butyl-4-hydroxy-2,5-dioxo-2H-pyrano[3,2-c]quinoline-3(6H)-carbaldehyde oxime (11). To a solution of enamine **2** (3.40 g, 10 mmol) in ethanol (25 mL), hydroxylamine hydrochloride (0.70 g, 10 mmol), was added. Then, the reaction mixture was refluxed for 8 h. The solid formed during heating was filtered off and crystallized from EtOH/H_2O to give compound **11** as yellow crystals (2.76 g, 84%), mp 214–215°C. IR (KBr, cm^{-1}) ν_{max}: 3322 (OH), 3088 (CH_{arom}), 2957, 2931, 2869 (CH_{aliph}), 1725 ($C{=}O_{\alpha\text{-pyrone}}$), 1690 ($C{=}O_{quinolone}$), 1627 (C=N). 1590 (C=C). ^{1}H NMR (DMSO-d_6) δ_H: 0.91 (t, 3H, J = 8.0 Hz, CH_2CH_3), 1.37–1.40 (m, 2H, CH_2CH_3), 1.55–1.57 (m, 2H, CH_2CH_2), 4.20 (t, 2H, J = 8.0 Hz, NCH_2), 7.41 (t, 1H, J = 7.6 Hz, H-9), 7.73 (d, 1H, J = 8.1 Hz, H-7), 7.96 (t, 1H, J = 7.6 Hz, H-8), 8.12 (d, 1H, J = 7.8 Hz, H-10), 9.63 (s, 1H, N=CH), 10.20 (s, 1H, OH), 11.58 (s, 1H, OH). ^{13}C NMR (125 MHz, DMSO-d_6) δ_C: 14.12 (CH_3), 19.94 (CH_2), 29.65 (CH_2), 42.08 (NCH_2), 100.45, 116.15, 116.40, 123.84, 124.10, 124.50, 128.86, 134.93, 138.45, 149.05, 159.36, 163.04, 179.99. MS: m/z (relative intensity): 329 [M^++ 1; 2], 328 [M^+; 11], 311 (4), 310 (20), 302 (18), 295 (5), 286 (10), 271 (19), 253 (12), 242 (24), 240 (7), 215 (55), 189 (37), 186 (23), 172 (10), 171 (30), 132 (41), 90 (5), 77 (100). *Anal*. Calcd for $C_{17}H_{16}N_2O_5$ (328.33): C, 62.19; H, 4.91; N, 8.53. Found: C, 62.23; H, 4.94; N, 8.54%.

6-Butyl-4-hydroxy-2,5-dioxo-2H-pyrano[3,2-c]quinoline-3(6H)-carbonitrile (12). A mixture of oxime **11** (3.28 g, 10 mmol) in glacial acetic acid (25 mL) was refluxed for 4 h. The solid so obtained after cooling was filtered and crystallized from ethanol to give compound **12** as pale yellow crystals (2.55 g, 82%), mp 214–215°C. IR (KBr, cm^{-1}) ν_{max}: 3415 (OH), 3043 (CH_{arom}), 2959, 2924, 2872 (CH_{aliph}), 2200 (C≡N), 1720 ($C{=}O_{\alpha\text{-pyrone}}$), 1674 ($C{=}O_{quinolone}$), 1605 (C=N), 1580 (C=C). ^{1}H NMR (DMSO-d_6) δ_H: 1.01 (t, 3H, J = 8.0 Hz, CH_2CH_3), 1.49–1.52 (m, 2H, CH_2CH_3), 1.75–1.77 (m, 2H, CH_2CH_2), 4.33 (t, 2H, J = 8.0 Hz, NCH_2), 7.44–7.46 (m, 2H, H-9 and H-7), 7.65 (t, 1H, J = 8.2 Hz, H-8), 8.23 (d, 1H, J = 8.1 Hz, H-10), 12.38 (s, 1H, OH). ^{13}C NMR (125 MHz, DMSO-d_6) δ_C: 14.09 (CH_3), 19.89 (CH_2), 29.58 (CH_2), 42.36 (NCH_2), 94.99 (C≡N), 105.45, 116.52, 116.74, 123.69, 124.90, 125.73, 127.23, 135.73, 146.17, 156.49, 162.97, 164.16. MS: m/z (relative intensity): 311 [M^++ 1; 11], 310 [M^+; 31], 293 (23), 285 (16), 284 (47), 268 (36), 256 (16), 254 (48), 242 (41), 241 (17), 240 (39), 229 (17), 228 (74), 215 (44), 212 (2), 201 (88), 188 (97), 187 (34), 172 (16), 159 (11), 132 (100), 119 (30), 116 (12), 104 (26), 90 (16), 77 (68). *Anal*. Calcd for $C_{17}H_{14}N_2O_4$ (310.31): C, 65.80; H, 4.55; N, 9.03. Found: C, 65.77; H, 4.52; N, 9.04%.

General procedure for formation of amino(pyrazolo- and isoxazolo-) [3′,4′:4,5]pyrano[3,2-*c*]quinolinones (13a–c). A mixture of compound **12** (3.10 g, 10 mmol) and 1,2-binucleophiles, *viz*. hydrazine hydrate (0.50 mL, 10 mmol), phenyl hydrazine (1.0 mL, 10 mmol), hydroxylamine hydrochloride (0.70 g, 10 mmol) in glacial acetic acid (50 mL) was heated under reflux for 4 h. After cooling to room temperature, the precipitate so formed was filtered off and crystallized from the proper solvent to give compounds **13a**–**c**.

1-Amino-5-butyl-3H-pyrazolo[3′,4′:4,5]pyrano[3,2-c]quinoline-4,11(5H)-dione (13a). Crystallized from AcOH to give compound **13a** as yellow crystals (2.75 g, 85%), mp

188–189°C. IR (KBr, cm^{-1}) ν_{max}: 3526, 3368 (NH_2), 3228, 3170 (NH), 3018 (CH_{arom}), 2965, 2872, 2837 (CH_{aliph}), 1726 ($C{=}O_{\alpha\text{-pyrone}}$), 1679 ($C{=}O_{quinolone}$), 1568 (C=C). ^1H NMR (DMSO-d_6) δ_H: 0.90 (t, 3H, J = 8.0 Hz, CH_2CH_3), 1.36–1.39 (m, 2H, CH_2CH_3), 1.55–1.57 (m, 2H, CH_2CH_2), 4.19 (t, 2H, J = 8.0 Hz, NCH_2), 7.19 (s, 2H, NH_2), 7.35 (t, 1H, J = 8.4 Hz, H-8), 7.67 (d, 1H, J = 8.2 Hz, H-6), 7.96 (t, 1H, J = 8.4 Hz, H-7), 8.11 (d, 1H, J = 8.4 Hz, H-9), 10.24 (s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6) δ_C: 13.73 (CH_3), 20.12 (CH_2), 29.55 (CH_2), 42.42 (NCH_2), 100.09, 101.65, 113.69, 115.17, 124.21, 124.81, 134.07, 137.99, 156.99, 159.79, 162.70, 162.89, 169.11. MS: *m/z* (relative intensity): 324 [M^+; 1], 308 (1), 296 (1), 295 (2), 284 (1), 283 (1), 282 (1), 269 (2), 268 (1), 267 (1), 256 (2), 252 (1), 228 (2), 215 (100), 201 (4), 160 (11), 159 (95), 158 (12), 132 (15), 131 (53), 119 (4), 116 (10), 105 (26), 104 (35), 77 (55). *Anal*. Calcd for $C_{17}H_{16}N_4O_3$ (324.34): C, 62.95; H, 4.97; N, 17.27. Found: C, 62.92; H, 5.00; N, 17.30%.

1-Amino-5-butyl-3-phenylpyrazolo[3′,4′:4,5]pyrano[3,2-c] quinoline-4,11(5H)-dione (13b). Crystallization from DMF gave compound **13b** as white crystals (3.12 g, 78%), mp 211–212°C. IR (KBr, cm^{-1}) ν_{max}: 3487, 3398 (NH_2), 3049 (CH_{arom}), 2961, 2925, 2869 (CH_{aliph}), 1709 ($C{=}O_{\alpha\text{-pyrone}}$), 1679 ($C{=}O_{quinolone}$), 1606 (C=N), 1560 (C=C). ^1H NMR (DMSO-d_6) δ_H: 0.92 (t, 3H, J = 8.1 Hz, CH_2CH_3), 1.41–1.44 (m, 2H, CH_2CH_3), 1.63–1.65 (m, 2H, CH_2CH_2), 4.33 (t, 2H, J = 8.1 Hz, NCH_2), 6.98 (s, 2H, NH_2), 7.45 (t, 1H, J = 7.4 Hz, Ar–H), 7.56 (d, 1H, J = 8.3 Hz, Ar–H), 7.75–7.77 (m, 2H, Ar–H), 7.84–7.88 (m, 2H, Ar–H), 8.05 (d, 1H, J = 8.1 Hz, Ar–H), 8.15 (t,1H, J = 8.4 Hz, Ar–H), 8.24 (d, 1H, J = 8.1 Hz, Ar–H). ^{13}C NMR (125 MHz, DMSO-d_6) δ_C: 13.75 (CH_3), 20.17 (CH_2), 29.56 (CH_2), 42.49 (NCH_2), 100.47, 113.81, 114.12, 115.11, 115.84, 124.13, 124.51, 124.84, 127.67, 132.56, 133.83, 137.93, 154.94, 156.20, 157.60, 161.48, 161.55, 163.17, 164.08. MS: *m/z* (relative intensity): 401 [M^++ 1; 3], 400 [M^+; 10], 371(18), 372 (66), 344 (24), 343 (100), 328 (5), 315 (48), 300 (7), 268 (2), 241 (4), 240 (5), 216 (44), 204(6), 189 (85), 188 (58), 187 (10), 172 (8), 161 (77), 159 (4), 133 (24), 132 (80), 104 (24), 77 (65). *Anal*. Calcd for $C_{23}H_{20}N_4O_3$ (400.44): C, 68.99; H, 5.03; N, 13.99. Found: C, 68.80; H, 5.11; N, 13.95%.

1-Amino-5-butyl-4H-isoxazolo[5′,4′:4,5]pyrano[3,2-c]quinoline-4,11(5H)-dione (13c). Recrystallized from DMF affording **13c** as yellow crystals (2.79 g, 86%), mp 245–246°C. IR (KBr, cm^{-1}) ν_{max}: 3492, 3394 (NH_2), 3045 (CH_{arom}), 2961, 2925, 2869 (CH_{aliph}), 1709 ($C{=}O_{\alpha\text{-pyrone}}$), 1679 ($C{=}O_{quinolone}$), 1606 (C=N), 1560 (C=C). ^1H NMR (DMSO-d_6) δ_H: 1.01 (t, 3H, J = 8.0 Hz, CH_2CH_3), 1.47–1.49 (m, 2H, CH_2CH_3), 1.78–1.81 (m, 2H, CH_2CH_2), 4.33 (t, 2H, J = 8.0 Hz, NCH_2), 7.20 (s, 2H, NH_2), 7.46 (t, 1H, J = 8.1 Hz, H-8), 7.67 (d, 1H, J = 7.4 Hz, H-6), 7.78 (t, 1H, J = 8.1 Hz, H-7), 8.24 (d, 1H, J = 8.1 Hz, H-9). ^{13}C NMR (100.6 MHz, DMSO-d_6) δ_C: 14.03 (CH_3), 19.92 (CH_2), 29.70 (CH_2), 42.35 (NCH_2), 99.87, 102.63, 113.72, 115.88, 116.67, 123.95, 124.64, 134.41, 138.09, 157.35, 160.08, 163.31, 163.85. MS: *m/z* (relative intensity): 326 [M^++ 1; 42], 325 [M^+; 100], 299 (22), 283 (2), 282 (99), 280 (17), 255 (19), 254 (10), 228 (9), 99 (15). *Anal*. Calcd for $C_{17}H_{15}N_3O_4$ (325.33): C, 62.76; H, 4.65; N, 12.92. Found: C, 62.75; H, 4.55; N, 12.90%.

General procedure for formation of aminopyrimidopyrano[3,2-*c*]quinolinone (14a–c). A mixture of compound **12** (3.10 g, 10 mmol) and guanidine hydrochloride (0.95 g, 10 mmol), acetamidine hydrochloride (0.95 g, 10 mmol), or thiourea (0.76 g, 10 mmol) in DMF (50 mL) was refluxed for 4 h. The solid obtained after cooling was filtered and crystallized from the proper solvent to afford compounds **14a–c**.

1,3-Diamino-6-butyl-5H-pyrimido[4′,5′:4,5]pyrano[3,2-c] quinoline-5,12(6H)-dione (14a). Crystallized from DMF to give **14a** as yellow crystals (2.39 g, 68%), mp 190–191°C. IR (KBr, cm^{-1}) ν_{max}: 3526, 3380 (NH_2), 3200, 3175 (NH), 3006 (CH_{arom}), 2959, 2918, 2848 (CH_{aliph}), 1722 ($C{=}O_{\alpha\text{-pyrone}}$), 1666 ($C{=}O_{quinolone}$), 1613 (C=N), 1572 (C=C). ^1H NMR (DMSO-d_6) δ_H: 0.92 (t, 3H, J = 8.0 Hz, CH_2CH_3), 1.41–1.43 (m, 2H, CH_2CH_3), 1.63–1.65 (m, 2H, CH_2CH_2), 4.31 (t, 2H, J = 8.0 Hz, NCH_2), 6.97 (s, 2H, NH_2), 7.45 (t, 1H, J = 8.0 Hz, H-9), 7.74 (d, 1H, J = 8.0 Hz, H-7), 8.05 (t, 1H, J = 8.0 Hz, H-8), 8.10 (d, 1H, J = 8.0 Hz, H-10), 9.37 (s, 2H, NH_2). MS: *m/z* (relative intensity): 352 [M^++ 1; 2], 351 [M^+; 4], 381 (23), 254 (52), 226 (48), 159 (40), 135 (39), 132 (100), 103 (58), 91 (87). *Anal*. Calcd for $C_{18}H_{17}N_5O_3$ (351.37): C, 61.53; H, 4.88; N, 19.93. Found: C, 61.51; H, 4.85; N, 19.63%.

1-Amino-6-butyl-3-methyl-5H-pyrimido[4′,5′:4,5]pyrano[3, 2-c]quinoline-5,12(6H)-dione (14b). This compound formed yellow crystals (2.66 g, 76%), mp > 300°C and crystallized from AcOH. IR (KBr, cm^{-1}) ν_{max}: 3523, 3358 (NH_2), 3043 (CH_{arom}), 2958, 2932, 2872 (CH_{aliph}), 1705 ($C{=}O_{\alpha\text{-pyrone}}$), 1682 ($C{=}O_{quinolone}$), 1613(C=N), 1570 (C=C). ^1H NMR (DMSO-d_6) δ_H: 1.00 (t, 3H, J = 8.0 Hz, CH_2CH_3), 1.52–1.55 (m, 2H, CH_2CH_3), 1.76–1.78 (m, 2H, CH_2CH_2), 2.70 (s, 3H, CH_3), 4.36 (t, 2H, J = 8.0 Hz, NCH_2), 7.37 (bs, 2H, NH_2), 7.46–7.49 (m, 2H, H-9 and H-7), 7.71 (t, 1H, J = 8.2 Hz, H-8), 8.30 (d, 1H, J = 8.1 Hz, H-10). ^{13}C NMR (125 MHz, DMSO-d_6) δ_C: 13.80 (CH_2CH_3), 14.43 (CH_3), 20.27 (CH_2), 29.57 (CH_2), 42.52 (NCH_2), 100.82, 113.51, 114.89, 122.91, 123.16, 124.67, 124.94, 133.47, 138.77, 154.53, 156.15, 156.96, 157.13, 164.72. MS: *m/z* (relative intensity): 351 [M^++ 1; 62], 350 [M^+; 93], 322 (82), 279 (60), 278 (75), 268 (75), 263 (55), 250 (100),

237 (72), 211 (63), 183 (50), 160 (57), 159 (57), 158 (77), 132 (63), 118 (59), 104 (50), 91 (80), 77 (57). *Anal*. Calcd for $C_{19}H_{18}N_4O_3$ (350.38): C, 65.13; H, 5.18; N, 15.99. Found: C, 65.12; H, 5.20; N, 15.96%.

1-Amino-6-butyl-3-thioxo-3H,5H-pyrimido[4′,5′:4,5]pyrano [3,2-c]quinoline-5,12(6H)-dione (14c). Crystallized from DMF to afford **14c** as yellow crystals, (2.70 g, 73%), mp > 300°C. IR (KBr, cm^{-1}) ν_{max}: 3490, 3342 (NH_2), 3156 (NH), 2957, 2928, 2850 (CH_{aliph}), 1748 ($C{=}O_{\alpha\text{-pyrone}}$), 1679 ($C{=}O_{quinolone}$), 1617 (C=N), 1576 (C=C). ^{1}H NMR (DMSO-d_6) δ_H: 0.93 (t, 3H, J = 8.0 Hz, CH_2CH_3), 1.44–1.46 (m, 2H, CH_2CH_3), 1.65–1.67 (m, 2H, CH_2CH_2), 4.32 (t, 2H, J = 8.0 Hz, NCH_2), 7.00 (s, 2H, NH_2), 7.52 (t, 1H, J = 8.0 Hz, H-9), 7.76–7.78 (m, 2H, H-7 and H-8), 8.22 (d, 1H, J = 8.1 Hz, H-10), 12.28 (s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6) δ_C: 14.02 (CH_2CH_3), 19.92 (CH_2), 29.71 (CH_2), 42.34 (NCH_2), 99.89, 102.63, 113.71, 116.65, 123.94, 127.63, 134.39, 135.58, 138.08, 157.34, 160.08, 163.30, 163.83, 169.02. MS: m/z (relative intensity): 369 [M^++ 1; 3], 368 [M^+; 9], 352 [M^+− NH_2; 2], 236 (11), 279 (10), 147 (13), 124 (14), 113 (11), 95 (37), 57 (100). *Anal*. Calcd for $C_{18}H_{16}N_4O_3S$ (368.42): C, 58.68; H, 4.38; N, 15.21; S, 8.70. Found: C, 58.70; H, 4.33; N, 15.22; S, 8.72%.

1-Amino-6-butyl-3,5,12-trioxo-3H-pyrido[2′,3′:4,5]pyrano[3, 2-c]quinoline-2(6H)-carbonitrile (16). A solution of carbonitrile **12** (3.10 g, 10 mmol) in ethanol (25 mL) containing few drops of triethyl amine was treated with malononitrile (0.66 g, 10 mmol) under reflux conditions for 4 h. The solid so obtained after cooling was filtered and crystallized from DMF to give compound **16** as pale brown crystals, (3.23 g, 86%), mp 169–170°C. IR (KBr, cm^{-1}) ν_{max}: 3473, 3335 (NH_2), 3167 (NH), 2958, 2930, 2871 (CH_{aliph}), 2189 (CN), 1752 ($C{=}O_{\alpha\text{-pyrone}}$), 1669 ($C{=}O_{pyridone}$), 1636 ($C{=}O_{quinolone}$), 1612 (C=N), 1572 (C=C). ^{1}H NMR (DMSO-d_6) δ_H: 0.92 (t, 3H, J = 8.0 Hz, CH_2CH_3), 1.37–1.40 (m, 2H, CH_2CH_3), 1.61–1.63 (m, 2H, CH_2CH_2), 4.33 (t, 2H, J = 8.0 Hz, NCH_2), 7.32 (t, 1H, J = 8.1 Hz, H-9), 7.43 (d, 1H, J = 8.1 Hz, H-7), 7.56 (t, 1H, J = 8.1 Hz, H-8), 7.72 (s, 2H, NH_2), 8.03 (d, 1H, J = 8.1 Hz, H-10), 13.15 (s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6) δ_C: 13.82 (CH_3), 20.18 (CH_2), 29.52 (CH_2), 42.61 (NCH_2), 89.38, 107.37, 113.09, 114.92, 122.74, 123.00, 124.29, 125.02, 133.84, 139.68, 141.12, 147.63, 156.86, 158.89, 164.49, 170.61. MS: m/z (relative intensity): 377 [M^++ 1; 5], 376 [M^+; 32], 350 [M^+− CN; 15] (4), 334 (31), 269 (40), 188 (15), 160 (2), 158 (13), 132 (100), 119 (5), 91 (11), 77 (30). *Anal*. Calcd for $C_{20}H_{16}N_4O_4$ (376.37): C, 63.83; H, 4.28; N, 14.89. Found: C, 63.85; H, 4.30; N, 14.90%.

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