Substituted Quinolinones. Part 13
A Convenient Route to Heterocyclization Reactions with 3-Substituted 4-Hydroxyquinolin-2(1*H*)-one

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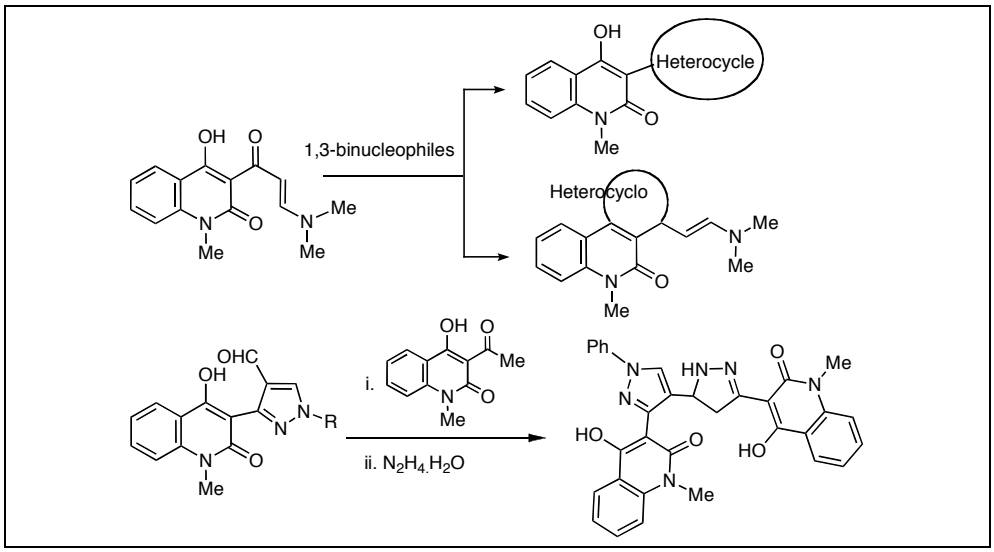

The reactivity of 3-[(dimethylamino)prop-2-enoyl]-4-hydroxyl-1-methylquinolin-2(1*H*)-one (**2**) towards different nucleophilic and electrophilic reagents was investigated. The convenient synthesis of several 3-heterocyclyl-quinolinones such as 3-pyridazinyl- **10**, **11**, 3-pyranyl **19a,b** and 3-pyrazolylquinolinones **20a,b**, **22**, **26a,b**, **27a,b**, **31** and **33** has been described starting from the 3-acetylquinolinone **1** and enaminone **2**. In addition, certain heterocyclo[*c*]quinolinones such as pyrimido- **12**, **14** pyrano- **3**, **17a,b** and pyrazolopyranoquinolinone **29** were obtained in good yields.

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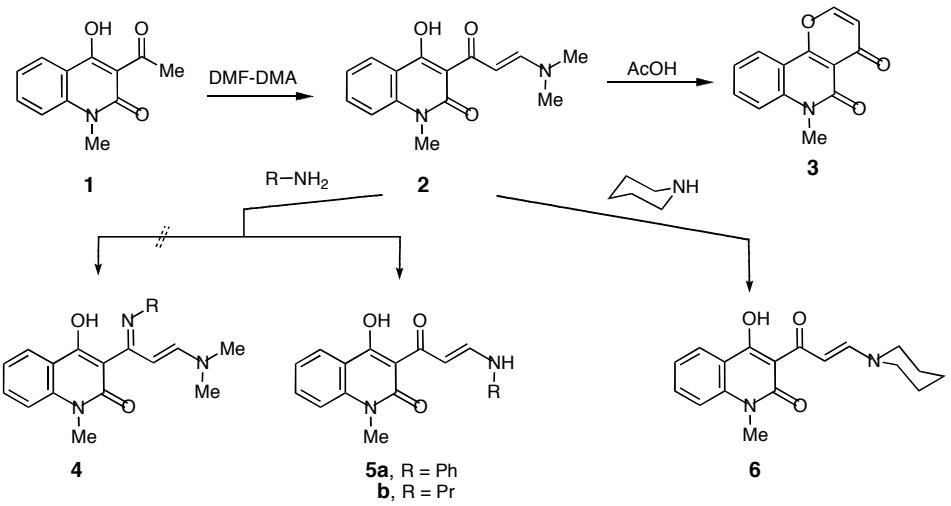
Quinolin-2-ones represent one of the most active classes of heterocyclic compounds possessing a wide variety of significant medicinal, pharmacological, and industrial applications [1-4]. Due to these important applications of quinolinone derivatives and in continuation of our program, devoted for studying the chemistry of biologically active quinolin-2-ones and enaminones [2,5-8], prompted our interest to explore the reactivity of 4-hydroxyquinolin-2-one bearing an electron push-pull enaminone side chain moiety at position 3. The chemical behavior of this system was checked towards different reagents at the purpose of production of new substituted quinolinones. This work describes the synthetic utility of the newly prepared enaminone **2** [2], which is leading to several hetero-aromatic ring systems as fused or substituents at the quinolinone moiety of expected biological activity.

The starting compound 3-[(2*E*)-3-(dimethylamino)-prop-2-enoyl]-4-hydroxy-1-methyl-quinolin-2(1*H*)-one (**2**) was smoothly obtained *via* thermal condensation of 3-acetyl-4-hydroxyl-1-methylquinolin-2(1*H*)-one (**1**) [9] with dimethylformamide dimethylacetal (DMF-DMA) [2,7]. This enaminone **2** when boiled in glacial acetic acid underwent an intramolecular cyclo-condensation furnishing a crystalline material that was characterized as 6-methyl-4*H*-pyrano[3,2-*c*]quinoline-4,5(6*H*)-dione (**3**).

Two primary amines *viz.* aniline and propylamine were taken as examples to check the nucleophilic condensation behavior of the enaminone **2**. Interestingly, two structures are probable; enaminoimine **4** and enaminone **5**. However, in glacial acetic acid at room temperature the reaction afforded only the derivatives **5a,b**. Structure **4** was ruled out on basis of the ^{1}H nmr spectrum which confirmed the absence of two signals at $\delta \approx 3.0–3.5$ ppm which characterize the NMe_2 grouping. The ease of removal NMe_2 moiety was also achieved by treatment of enaminone **2** with piperidine giving rise to the 2*E*-3-(piperidin-1-yl)prop-2-enone **6** (Scheme I).

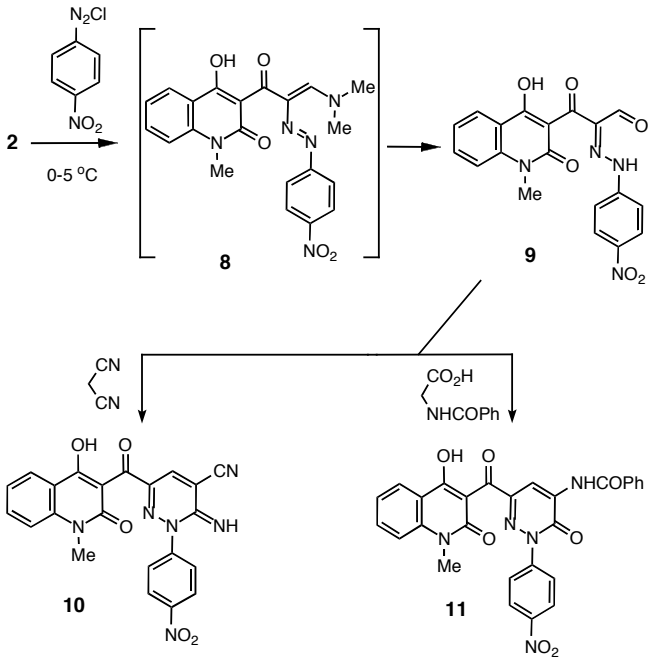
Scheme I



Combination of pyridazine and/or pyrimidine and quinolinone, in one molecular framework, is rarely reported in the literature. For this reason and because of the well-known biological activities of these ring systems, the enaminone **2** was employed as promising synthon for such targets. Thus, compound **2** smoothly coupled with 4-nitrobenzenediazonium chloride to produce the inseparable arylazo intermediate **8** [10], which is readily hydrolyzed in the reaction course to yield the α-hydrazono-β-oxopropanal **9**.

Cyclization of the hydrazone derivative **9** with malononitrile in the presence of piperidine furnished the 3-iminopyridazine-4-carbonitrile derivative **10**. The reaction of compound **9** with hippuric acid in acetic anhydride afforded the 4-benzoylamino-6-[(quinolin-3-yl)carbonyl]-pyridazin-3(2*H*)-one **11**, in 66% yield (Scheme II).

Scheme II

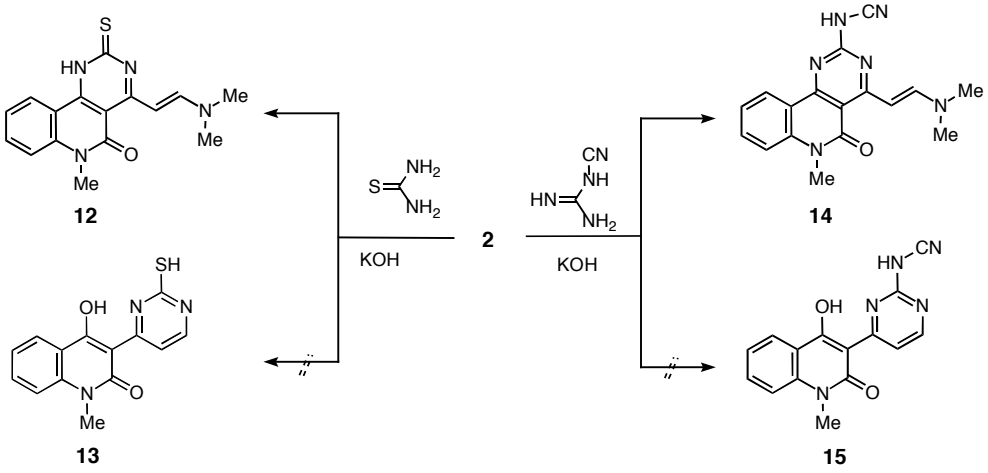


Moreover reaction of enaminone **2** with thiourea in ethanolic potassium hydroxide solution did not give the anticipated pyrimidinylquinolinone **13** and instead the pyrimido[5,4-*c*]quinolin-5(1*H*)-one **12** was afforded. Compound **12** gave negative ferric chloride test due to the absence of OH group. Also, ^{1}H nmr spectrum showed the presence of two singlets at δ = 3.30 and 3.45 ppm due to NMe_2, in addition to the characteristic signals of the *trans*-olefinic protons. Moreover, similar treatment of the enaminone **2** with cyanoguanidine gave another pyrimido[5,4-*c*]quinolinone derivative **14** and herein again the pyrimidinylquinolinone structure **15** was obviously excluded (Scheme III).

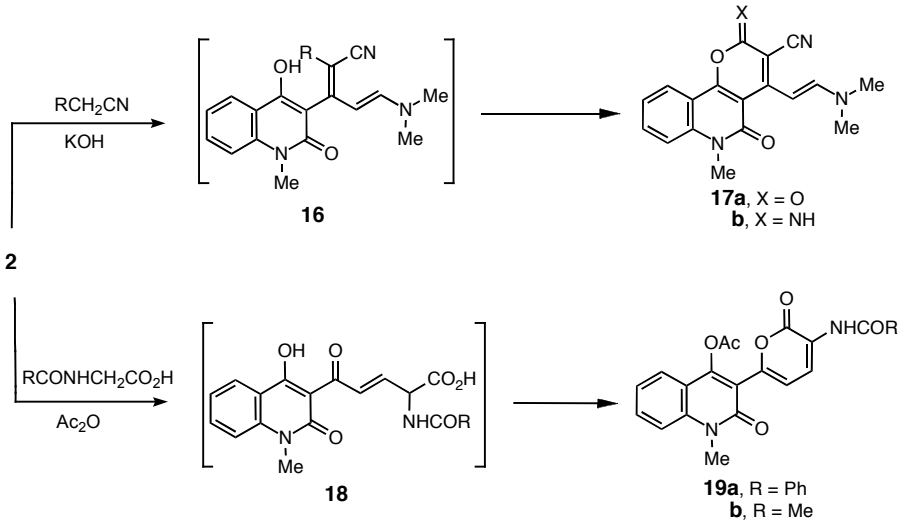
When the enaminone **2** was allowed to react with some active methylene compounds such as ethyl cyanoacetate and malononitrile in the presence of potassium hydroxide, the pyranoquinolinone derivatives **17a** (X = O) and **17b** (X = NH) were respectively obtained. The reaction of compound **2** with hippuric acid and/or aceturic acid in boiling acetic anhydride [13], afforded 4-acetoxy-3-[3-(benzoyl or acetyl)-amino-2-oxo-2*H*-pyran-6-yl]-1-methyl-quinolin-2(1*H*)-ones **19a,b** (R = Ph, Me). The spectral data revealed disappearance of dimethylaminovinyl system and the structure **19** indicated that the cyclization process does not involve the hydroxyl group at position-4 of quinolinone (Scheme IV).

Both the acetyl **1** and enaminone **2** derivatives of 4-hydroxyquinolinone are considered as appropriate intermediates for pyrazole heterocyclization reactions. Thus, treatment of the compound **2** with thiosemicarbazide and thiocarbodihydrazide furnished the 1*H*-pyrazole-1-carbothioamide **20a** and 1*H*-pyrazole-1-carbothiohydrazide **20b**, respectively. Cyclo-condensation of 7-chloro-4-hydrazinoquinoline (**21**) with the enaminone **2**, in glacial acetic acid, afforded 4-hydroxyl-1-methyl-3-[1-(7-chloroquinolin-4-yl)-1*H*-pyrazol-3-yl]quinolin-2(1*H*)-one (**22**). The structure

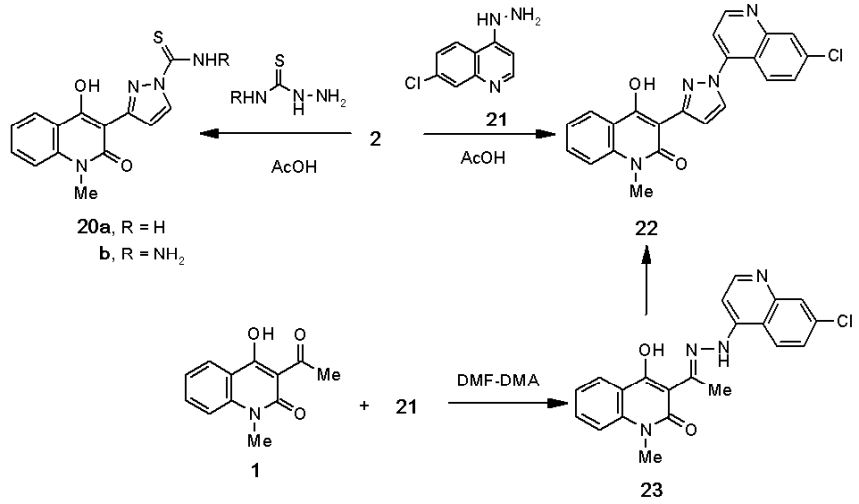
Scheme III



Scheme IV



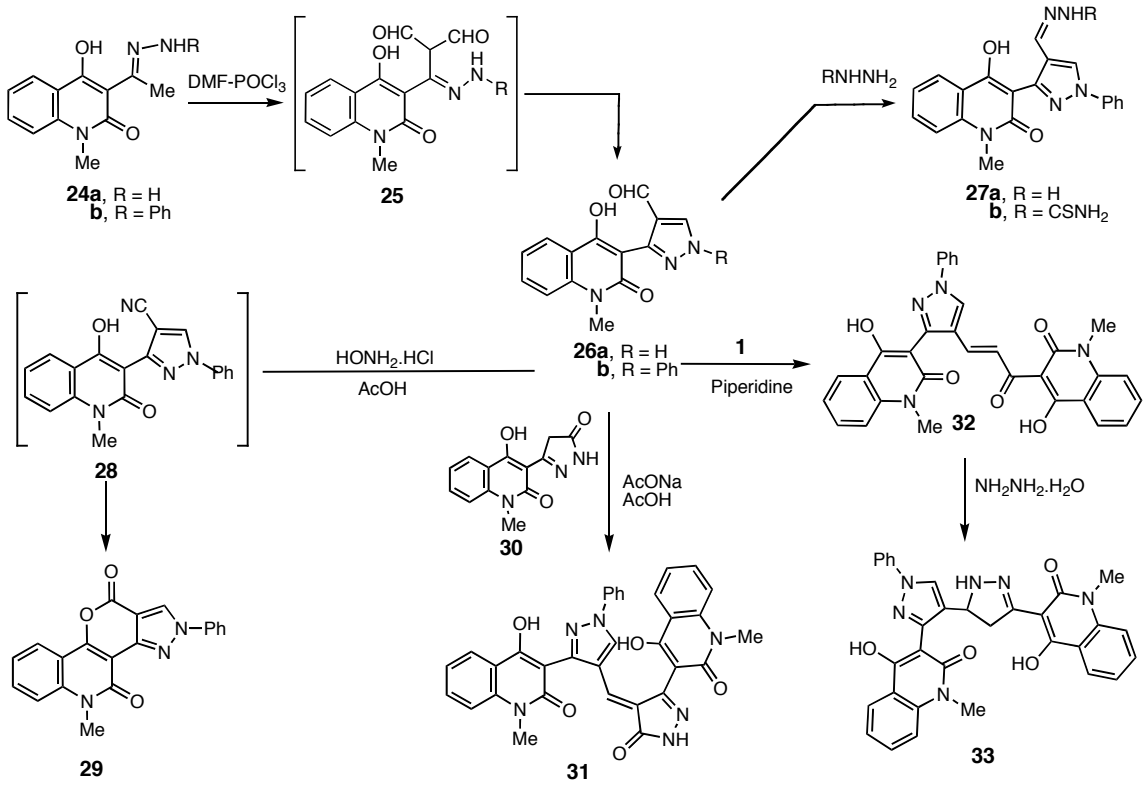
Scheme V



suggested for the compound **22** was chemically fortified by its alternative synthesis starting from the acetylquinolinone **1**. Thus, the hydrazone **23** was obtained on treatment of the compound **1** with the compound **21**. In situ, thermal condensation of the hydrazone **23** with DMF-DMA smoothly led to the compound **22** (Scheme V).

linone, which in turn hydrolyzed to give the separated tetracyclic system **29**. Another possibility is the hydrolysis of the intermediate **28** into the corresponding carboxylic acid is responsible for the formation of the pyrone ring *via* an intramolecular condensation. Anyhow both routes are logical and possible.

Scheme VI



Condensation of the acetylquinolinone **1** with hydrazine hydrate and with phenylhydrazine afforded the respective hydrazones **24a,b** [11] (Scheme VI). The hydrazones **24a,b** were subjected to react with *Vilsmeier-Haack* reagent (DMF-$POCl_3$) [12] to give the substituted pyrazole-4-carbaldehydes **26a** (R = H) and **26b** (R = Ph) through the intermediacy of the corresponding 3-(1-hydrazono-2,2-diformylethyl)quinolinone **25**. Traditional condensation reaction of the aldehyde **26b** with hydrazine hydrate and thiosemicarbazide yielded the hydrazone **27a** (R = H) and thiosemicarbazone **27b** (R = $CSNH_2$), respectively in good yields. Surprisingly, the condensation of **26b** with hydroxylamine hydrochloride, in glacial acetic acid did not give the expected oxime or even the probable carbonitrile **28**. The compound that separated from the latter reaction was characterized as 6-methyl-16-phenyl-16*H*-pyrazolo-[3',4':4,5]pyrano[3,2-*c*]quinoline-7, 12(6*H*)-dione (**29**) (Scheme VI). It seems that successive steps took place in which condensation leading to the oxime is followed by dehydration to the carbonitrile **28**. Afterwards the carbonitrile underwent cycloaddition to an iminopyranoquino-

Selectively, we carried out *Knoevenagel* condensation reaction of the aldehyde **26b** with the pyrazolinone **30** [13] as an active methylene compound possessing both quinolinone and pyrazole nuclei in the same molecule. This reaction led to facile synthesis of the newly isolated tetracyclic system **31**. Attractively, another system of this category was prepared in two steps. Thus, the condensation of the available acetylquinolinone **1** with the aldehyde **26b** gave the α,β-unsaturated ketone **32**, which was treated with hydrazine hydrate to form the polynuclear heterocyclic compound **33** having two quinolinone and two pyrazole moieties in one molecular frame (Scheme VI).

EXPERIMENTAL

All melting points were measured on a Gallenkamp MFB-595 apparatus and are uncorrected. IR spectra were recorded on Perkin-Elmer FT-IR 1650 spectrophotometer in KBr disks. ^1H and ^{13}C nmr spectra were recorded on a Varian Gemini 400 MHz (at 100.58 MHz for ^{13}C) instrument, using either $CDCl_3$ or DMSO-d_6 as solvents and TMS as an internal standard. Mass

spectra were obtained on HP MS-5988 and Carlo–Erba QMD-1000 instrument by direct inlet, at beam energy 70 eV. Elemental analyses were carried out on Perkin-Elmer 2400 Analyzer or at Cairo University Microanalytical Centre and Ain Shams University Analytical Unit. Silica gel plates (Merck F254) and silica gel 60 (Merck 230-400 mesh) were used for analytical TLC and for flash chromatography, respectively. 3-Acetyl-4-hydroxy-1-methylquinolin-2(1*H*)-one (**1**) [9], 1-(4-hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)-3-dimethyl-amino-2-propen-1-one (**2**) [2,7], and 3-[1-(hydrazono and phenylhydrazono)-ethyl]-4-hydroxy-1-methylquinolin-2(1*H*)-ones **24a,b** [11] were prepared according to the literature methods.

6-Methyl-4*H*-pyrano[3,2-*c*]quinoline-4,5(6*H*)-dione (3). The compound **2** (10 mmol) was refluxed in glacial acetic acid (20 mL) for 2 h, and then left to cool to room temperature. The precipitated crystalline material was filtered, washed with ethanol, dried, and recrystallized from DMSO, in 90% yield, m.p. 225-227 °C; IR (KBr): ν_{max} 1660 ($C=O_{pyrone}$), 1640 ($C=O_{quinolone}$), 1600, 1592 cm^{-1}; MS (EI, 70 eV): *m/z* (*I*%) 227 (100) (M^+), 201 (66.23) ($M^+ - C_2H_2$), 199 (57.73) ($M^+ - CO$), 175 (78.05) ($M^+ - C_2HO^•$), 104 (53.00) ($CH_2=N-C_6H_4^+$), 77 (58.77) ($C_6H_5^+$). *Anal.* Calcd. for $C_{13}H_9NO_3$: C, 68.72; H, 3.99; N, 6.16 %. Found: C, 68.54; H, 3.77; N, 5.98.

General Procedure for the Preparation of Enaminones 5a,b. To a solution of the compound **2** (10 mmol), in glacial acetic acid (20 mL), each of aniline and *n*-propylamine was added (10 mmol). The mixture was stirred at room temperature for 1 h. The precipitate so formed was filtered and purified by flash-chromatography by ethyl acetate/petroleum as eluent ether (1:2, v/v) and then crystallized from acetic acid.

3-[(2*E*)-3-Anilinoprop-2-enoyl]-4-hydroxy-1-methylquinolin-2(1*H*)-one (5a). This compound was obtained in 89.8% yield, m.p. 265-266 °C; IR (KBr): ν_{max} 3210 (NH), 2800-2700 (H-bonded OH), 1645 (C=Oquinolone), 1618, 1600, 1589; ^{1}H nmr (DMSO-d_6): δ_H 3.71 (s, 3H, NMe), 7.15-8.30 (m, 11H, H_{arom} + H_{olefin}), 11.60 (bs, 1H, NH); ^{13}C nmr (DMSO-d_6): δ_C 30,01, 96.98, 104.44, 114.01, 116.53, 116.78, 121.75, 124.34, 125.72, 129.84, 133.80, 139.90, 140.93, 146.41, 161.74, 173.56, 192.70; MS (EI, 70 eV): *m/z* (*I*%) 320 (7.33) (M^+), 228 (100), 202 (10.35), 145 (2.15), 134 (7.48), 118 (10.34), 77 (13.85). *Anal.* Calcd. for $C_{19}H_{16}N_2O_3$: C, 71.24; H, 5.03; N, 8.75 %. Found: C, 71.10; H, 4.86; N, 8.59.

4-Hydroxy-1-methyl-3-[(2*E*)-3-(propylamino)prop-2-enoyl]-quinolin-2(1*H*)-one (5b). This compound was obtained in 75% yield, m.p. 243-244 °C; IR (KBr): ν_{max} 3137 (NH), 2980 (CH_{aliph}), 2873-2850 (H-bonded OH), 1651 ($C=O_{quinolone}$), 1620, 1590 cm^{-1}; ^{1}H nmr ($CDCl_3$): δ_H 1.01 (t, 3H, CH_3), 1.59 (m, 2H, CH_2), 3.20 (q, 2H, CH_2), 3.60 (s, 3H, $NMe_{quinolone}$), 6.90-8.11 (m, 6H, H_{arom} + H_{olefin}), 9.76 (bs, 1H, NH); MS (EI, 70 eV): *m/z* (*I*%) 286 (34.06) (M^+), 228 (38.60), 202 (51.26), 175 (11.71), 134 (28.13), 77 (100). *Anal.* Calcd. for $C_{16}H_{18}N_2O_3$: C, 67.12; H, 6.34; N, 9.79 %. Found: C, 67.01; H, 6.09; N, 9.52.

4-Hydroxy-1-methyl-3-[(2*E*)-3-(piperidin-1-yl)prop-2-enoyl]-quinolin-2(1*H*)-one (6). A suspension of the compound **2** (10 mmol) was treated with piperidine (10 mmol), and then heated under reflux for 3h. The crystalline precipitate so formed during the course of the reaction was collected by filtration and recrystallized from acetic acid, in 68% yield, m.p. 222-224 °C; IR (KBr): ν_{max} 2916 (CH_{aliph}), 2860 (OH), 1654 (C=O), 1646 (C=O), 1626, 1595 cm^{-1}; ^{1}H nmr ($CDCl_3$): δ_H 1.50 (m, 6H, $(CH_2)_3$), 3.58 (m, 4H, CH_2-N-CH_2), 3.64 (s, 3H, NMe), 7.21-736 (m, 3H, H_{arom} + H_{olefin}), 7.63 (t, 1H, C7-H), 8.16 (d, *J*,*J* = 15 Hz,1H, H_{olefin}), 8.24 (d, *J*,*J* = 8 Hz, 1H, C5-H); MS (EI, 70 eV): *m/z* (*I*%) 312 (22.19) (M^+), 294 (13.19), 228 (51.07), 202 (4.95), 134 (5.54), 110 (100), 105 (7.56). *Anal.* Calcd. for $C_{19}H_{16}N_2O_3$: C, 67.21; H, 6.45; N, 8.72 %. Found: C, 67.14; H, 6.19; N, 8.69.

(2*E*)-3-(4-Hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)-2-[(4-nitrophenyl)hydrazono]-3-oxopropanal (9). A cold solution of 4-nitrobenzenediazonium chloride (10 mmol) (prepared by adding a solution of 1.5 g sodium nitrite in 10 mL H_2O to a cold solution of 4-nitroaniline in 5 mL concentrated HCl) was added with continuous stirring to a cold solution of enaminone **2** in ethanol (50 mL, 95%) containing sodium hydroxide (20 mmol). The mixture was stirred at room temperature for 1 h and the solid product, so formed, was collected by filtration, dried, and crystallized from DMF, in 75% yield, m.p. 237-239 °C; IR (KBr): ν_{max} 3390-2780 (br, NH + OH), 1700 ($C=O_{aldeyde}$), 1650 ($C=O_{quinolone}$), 1620 (C=N), 1603, 1588 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ_H 3.60 (s, 3H, NMe), 6.40 (s, 1H, NH), 7.30-8.30 (m, 8H, H_{arom}), 8.65 (s, 1H, CH=O); MS (EI, 70 eV): *m/z* (*I*%) 394 (5.00) (M^+), 385 (2.42), 365 (7.00), 257 (28.80), 202 (100), 175 (17.05), 146 (8.40), 105 (18.13), 104 (19.40), 77 (21.05). *Anal.* Calcd. for $C_{19}H_{14}N_4O_6$: C, 64.46; H, 4.16; N, 11.56 %. Found: C, 64.29; H, 4.01; N, 11.38.

6-[(4-Hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)-carbonyl]-3-imino-2-(4-nitrophenyl)-2,3-dihydropyridazine-4-carbonitrile (10). To a suspension of the propanal **9** (10 mmol), in absolute ethanol (30 mL), malononitrile (10 mmol) and a few drops of piperidine were added. The mixture was heated under reflux for 6 h, left to cool to room temperature, and then poured into water. The solid product that formed was purified by flash-chromatography using ethyl acetate/ petroleum ether as eluent (1:1, v/v) and then crystallized from ethanol, in 55% yield, m.p. 280-282 °C; IR (KBr): ν_{max} 3419-3000 (br, OH, NH), 2211 (C≡N), 1655 ($C=O_{ketone}$), 1643 ($C=O_{quinolone}$), 1620 (C=N), 1550 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ_H 3.65 (s, 3H, NMe), 5.85 (s, 1H, NH), 7.30-8.30 (m, 9H, H_{arom}); MS (EI, 70 eV): *m/z* (*I*%) 442 (357.41) (M^+), 433 (42.35), 277 (32.30), 185 (51.07), 134 (33.29), 105 (53.70) , 91 (100), 77 (53.33). *Anal.* Calcd. for $C_{22}H_{14}N_6O_5$: C, 59.73; H, 3.16; N, 19.00 %. Found: C, 59.58; H, 3.00; N, 18.87.

4-Benzoylamino-6-[(4-hydroxy-1-methyl-2-oxo-1,2-dihydro-quinolin-3-yl)carbonyl]-2-(4-nitrophenyl)pyridazin-3(2H)-one (11). A mixture of the propanal **9** (10 mmol), hippuric acid (10 mmol), and acetic anhydride (20 mL) was heated under reflux for 2 h. The excess solvent was evaporated under reduced pressure in vacuum. The pasty residue obtained was triturated with ethanol (25 mL), and the solidified material was collected by filtration, washed thoroughly with diethyl ether (25 mL) and crystallized from acetic acid, in 66% yield, m.p. >300 °C; IR (KBr): ν_{max} 3300, 3150-3077 (br, NH, OH), 1655 ($C=O_{ketone}$), 1647 ($C=O_{amide}$), 1619 (C=N), 1562 cm^{-1}; MS (EI, 70 eV): *m/z* (*I*%) 537 (4.10) (M^+), 432 (4.47) ($M^+ - C_6H_5CHO$), 335 (22.23) ($M^+ - C_{11}H_8NO_3$), 312 (2.15), 277 (9.80), 105 (100) ($C_6H_5C≡O^+$). *Anal.* Calcd. for $C_{28}H_{19}N_5O_7$: C, 62.57; H, 3.56; N, 13.03 %. Found: C, 62.33; H, 3.28; N, 12.76.

General Procedure for the Preparation of Pyrimido-quinolinones 12, 14 and Pyranoquinolinones 17a,b. Equimolar amounts (10 mmol) of the compound **2** and each of thiourea, cyanoguanidine, malononitrile, and ethyl cyanoacetate, in absolute ethanol (20 mL), were treated with potassium hydroxide (20 mmol) and then heated under reflux for 3 h. Afterwards, neutralization of the reaction mixture with dilute

acetic acid gave a precipitate which was filtered off, washed with water and purified by flash-chromatography using ethyl acetate/petroleum ether as eluent (1:2, v/v) and then crystallized from the proper solvent.

4-[(*E*)-2-(Dimethylamino)vinyl]-6-methyl-2-thioxo-2,6-dihydropyrimido[5,4-*c*]quinolin-5(1*H*)-one (12). This compound was obtained in 65% yield, m.p. 190-192 °C (ethanol); IR (KBr): ν_{max} 3150 (NH), 2925 (CH_{aliph}), 1650 ($C{=}O_{quinolone}$), 1618 (C=N), 1607, 1590, 1212, 1140 cm^{-1} (C=S); ^1H nmr ($CDCl_3$): δ_H 3.30, 3.45 (two s, 6H, NMe_2), 3.69 (s, 3H, $NMe_{quinolone}$), 6.29 (s, 1H, NH), 7.16- 8.3 (m, 6H, H_{arom} + H_{olefin}). *Anal.* Calcd. for $C_{16}H_{16}N_4OS$: C, 61.52; H, 5.16; N, 17.93 %. Found: C, 61.28; H, 5.01; N, 17.77.

4-[(*E*)-2-(Dimethylamino)vinyl]-6-methyl-5-oxo-5,6-dihydropyrimido[5,4-*c*]quinolin-2-ylcyanamide (14). This compound was obtained in 60% yield, m.p. 202-204 °C (acetone); IR (KBr): ν_{max} 3212(NH), 2950-2900 (CH_{aliph}), 2200 (C≡N), 1651 ($C{=}O_{quinolone}$), 1620, 1590 cm^{-1}; ^1H nmr (DMSO-d_6): δ_H 3.20, 3.40 (two s, 6H, NMe_2), 3.46 (s, 3H, $NMe_{quinolone}$), 6.30 (b, 1H, NH), 7.21-8.4 (m, 6H, H_{arom} + H_{olefin}); MS (EI, 70 eV): *m/z* (*I*%) 320 (2.14) (M^+), 280 (2.41), 149 (3.58), 97 (4.97), 77 (2.39), 58 (100). *Anal.* Calcd. for $C_{17}H_{16}N_6O$: C, 63.74; H, 5.03; N, 26.23 %. Found: C, 63.55; H, 4.79; N, 25.98.

4-[(*E*)-2-(Dimethylamino)vinyl]-6-methyl-2,5-dioxo-5,6-dihydro-2*H*-pyrano[3,2-*c*]quinoline-3-carbonitrile (17a). This compound was obtained in 70% yield, m.p. 260-263 °C (dioxane); IR (KBr): ν_{max} 2919 (CH_{aliph}), 2223 (C≡N), 1689 ($C{=}O_{pyrone}$), 1645 ($C{=}O_{quinolone}$), 1600, 1590 cm^{-1}; ^1H nmr (DMSO-d_6): δ_H 3.10 (s, 3H, NMe), 3.30 (s, 3H, NMe), 3.65 (s, 3H, $NMe_{quinolone}$), 7.10-8.20 (m, 6H, H_{arom} + H_{olefin}). *Anal.* Calcd. for $C_{18}H_{15}N_3O_3$: C, 67.28; H, 4.71; N, 13.08 %. Found: C, 67.01; H, 4.38; N, 12.82.

4-[(*E*)-2-(Dimethylamino)vinyl]-2-imino-6-methyl-5-oxo-5,6-dihydro-2*H*-pyrano[3,2-*c*]quinoline-3-carbonitrile (17b). This compound was obtained in 66% yield, m.p. 282-283 °C (methanol); IR (KBr): ν_{max} 3435 (NH), 2923 (CH_{aliph}), 2203 (C≡N), 1655 ($C{=}O_{quinolone}$), 1600, 1585 cm^{-1}; ^1H nmr (DMSO-d_6): δ_H 3.42 (two s, 6H, NMe_2), 3.46 (s, 3H, $NMe_{quinolone}$), 7.20-8.20 (m, 5H, H_{arom}+ H_{olefin}), 8.61 (d, *J,J* = 15.5 Hz, 1H, H_{olefin}); MS (EI, 70 eV): *m/z* (*I*%) 320 (9.00) (M^+), 291 (4.57), 250 (1.13), 105 (1.40), 77 (1.36), 85 (8.95), 58 (100). *Anal.* Calcd. for $C_{18}H_{16}N_4O_2$: C, 67.49; H, 5.03; N, 17.49 %. Found: C, 67.35; H, 4.80; N, 17.22.

General Procedure for the Preparation of Pyranylquinolinones 19a,b. A solution of the enaminone **2** (10 mmol) and each of hippuric acid or aceturic acid (10 mmol), in acetic anhydride (10 mL), was heated under reflux for 2 h. The reaction mixture was concentrated and the crystalline product that obtained upon cooling was isolated by filtration and recrystallized from acetic acid.

4-Acetoxy-3-(3-benzoylamino-2-oxo-2*H*-pyran-6-yl)-1-methylquinolin-2(1*H*)-ones (19a). This compound was obtained in 85% yield, m.p. 226-228 °C; IR (KBr): ν_{max} 1694 ($C{=}O_{acetoxy}$), 1684 ($C{=}O_{pyrone}$), 1648 ($C{=}O_{amide}$), 1600, 1590 cm^{-1}; ^1H nmr ($CDCl_3$): δ_H 2.50 (s, 3H, COMe), 3.65 (s, 3H, NMe), 7.20-7.80 (m, 9H, H_{arom}), 7.90 (d, 1H, γ-CH_{pyrone}), 8.60 (d, 1H, β-CH_{pyrone}), 8.75 (s, 1H, NH). *Anal.* Calcd. for $C_{24}H_{18}N_2O_6$: C, 66.97; H, 4.22; N, 6.51 %. Found: C, 66.74; H, 3.98; N, 6.32.

4-Acetoxy-3-(3-acetylamino-2-oxo-2*H*-pyran-6-yl)-1-methylquinolin-2(1*H*)-ones (19b). This compound was obtained in 80% yield, m.p. 212-214 °C; IR (KBr): ν_{max} 1770 ($C{=}O_{acetoxy}$), 1703 ($C{=}O_{pyrone}$), 1680-1645 ($C{=}O_{amide}$), 1605, 1589 cm^{-1}; ^1H nmr (DMSO-d_6): δ_H 2.22 (s, 3H, NCOMe), 2.50 (s, 3H, OCOMe), 3.68 (s, 3H, NMe), 7.20-7.62 (m, 4H, H_{arom}), 7.71 (d, 1H, γ-CH_{pyrone}), 8.03 (s, 1H, NH), 8.30 (d, 1H, β-CH_{pyrone}); MS (EI, 70 eV): *m/z* (*I*%) 368 (17.25) (M^+), 326 (100), 284 (47.30), 256 (50.99), 227 (59.48), 202 (36.88), 175 (58.19), 149 (32.65), 104 (36.41), 77 (46.89). *Anal.* Calcd. for $C_{19}H_{16}N_2O_6$: C, 61.96; H, 4.38; N, 7.61 %. Found: C, 61.67; H, 4.08; N, 7.44.

General Procedure for the Preparation of Pyrazolylquinolinones 20a,b and 22. To a solution of the compound **2** (10 mmol), in glacial acetic acid (20 mL), was added 10 mmol of each of thiosemicarbazide, thiocarbodihydrazide, and 7-chloro-4-hydrazinoquinoline (**21**). The reaction mixture was heated under reflux for 4 h, cooled, and poured into crushed ice. The solid precipitate was collected by filtration, dried, purified by flash-chromatography using ethyl acetate/petroleum ether as eluent (1:2, v/v) and then crystallized from the proper solvent.

3-(4-Hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)-1*H*-pyrazole-1-carbothioamide (20a). This compound was obtained in 75% yield, m.p. 245-247 °C (acetic acid); IR (KBr): ν_{max} 3240-2800 (br, NH_2, OH), 1645 ($C{=}O_{quinolone}$), 1620, 1570, 1330, 1225 (N-C=S) cm^{-1}; MS (EI, 70 eV): *m/z* (*I*%) 300 (3.16) (M^+), 282 (2.47) (M^+–H_2O), 240 (5.27) (M^+–$CHSNH_2$), 149 (12.04), 104 (2.36) ($CH_2{=}NC_6H_4^+$), 83 (100) ($C_3H_5N_3^+$), 77 (3.97) ($C_6H_5^+$). *Anal.* Calcd. for $C_{14}H_{12}N_4O_2S$: C, 55.99; H, 4.03; N, 18.65 %. Found: C, 55.75; H, 3.86; N, 18.42.

3-(4-Hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)-1*H*-pyrazole-1-carbothiohydrazide (20b). This compound was obtained in 75% yield, m.p. 170-172 °C (DMF); IR (KBr): ν_{max} 3216-3450 (br, NH_2, NH, OH), 1650 ($C{=}O_{quinolone}$), 1627, 1577, 1326, 1160 (N-C=S) cm^{-1}; MS (EI, 70 eV): *m/z* (*I*%) 315 (75.00) (M^+), 240 (1.58), 212 (6.33), 175 (1.40), 146 (6.42), 104 (12.50), 77 (82.67), 76 (100). *Anal.* Calcd. for $C_{14}H_{13}N_5O_2S$: C, 53.32; H, 4.11; N, 22.22 %. Found: C, 52.99; H, 4.01; N, 22.11.

4-Hydroxyl-1-methyl-3-[1-(7-chloroquinolin-4-yl)-1*H*-pyrazol-3-yl]quinolin-2(1*H*)-one (22). *Method a*. This compound was obtained according to the above general procedure, in 80% yield, m.p. 212-214 °C (DMF).

Method b. To a solution of the acetylquinolinone **1** (10 mmol), in DMF (20 mL), 7-chloro-4-hydrazinoquinoline (**21**) (10 mmol) was added. The reaction mixture was heated under reflux for 1 h. A canary yellow crystalline precipitate of the hydrazone **23** was obtained which was not separated. DMF-DMA (6 mmol) was added and the reaction mixture was heated under reflux for 4 h. The solvent was remove by evaporation under reduced pressure and the solid residue was triturated with methanol (5 mL), filtered, dried and crystallized from DMF to give the compound **22**, in 74% yield, m.p. 212-213 °C (no depression in mixed m.p.); IR (KBr): ν_{max} 3320-2750 (br, H-bonded OH), 1643 ($C{=}O_{quinolone}$), 1625, 1551, 760 (C-Cl) cm^{-1}; MS (EI, 70 eV): *m/z* (*I*%) 402.5 (2.60) (M^+), 312 (32.08), 302 (42.41), 288 (52.72), 241 (63.85) (M^+– [7-chloroquinoline]$^•$), 68 (100) (1*H*-pyrazolium ion). *Anal.* Calcd. for $C_{22}H_{15}N_4O_2Cl$: C, 65.59; H, 3.73; N, 13.91 %. Found: C, 65.38; H, 3.57; N, 13.77.

General Procedure for the Preparation of the Aldehydes 26a,b. Phosphoryl chloride (30 mmol) was dropwisely added to a stirred, ice-bath cooled, DMF (30 mmol) for 10 min. The mixture was kept at 0 °C for 30 min and then a solution of each of the hydrazones **24a** and **24b** (10 mmol), in DMF (10 mL) was added dropwise. The reaction mixture was then stirred at room temperature for 1 h and then heated at 70-80 °C for 4 h. After cooling to room temperature, the mixture was poured onto crushed ice and neutralized with a cold potassium carbonate

solution. The product so deposited was filtered, washed with water, purified by flash-chromatography using ethyl acetate/petroleum ether as eluent (1:1, v/v) and then crystallized from the proper solvent.

3-(4-Hydroxy-1-methyl-1,2-dihydro-2-oxoquinolin-3-yl)-1*H*-pyrazole-4-carbaldehyde (26a). This compound was obtained in 30% yield, m.p. 240-243 °C (DMF); IR (KBr): ν_{max} 3226, 3162 (NH, OH), 1650 (CH=O) , 1640 (C=$O_{quinolone}$), 1618 (C=N), 1594 cm^{-1}; ^{1}H nmr (DMSO-*d*6): δH 3.75 (s, 3H, NMe), 7.33 (t, 1H, C6-H), 7.41 (d, 1H, C8-H), 7.66 (t, 1H, C7-H), 8.04 (d, 1H, C5-H), 8.07 (s, 1H, C5'-$H_{pyrazole}$), 9.76 (s, 1H, CH=O); MS (EI, 70 eV): *m/z* (*I*%) 269 (40.52) (M^+), 252 (13.88), 202 (6.69), 105 (13.25), 73 (100). *Anal.* Calcd. for $C_{14}H_{11}N_3O_3$: C, 62.45; H, 4.12; N, 15.61 %. Found: C, 62.23; H, 3.85; N, 15.51.

3-(4-Hydroxy-1-methyl-1,2-dihydro-2-oxoquinolin-3-yl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde (26b). This compound was obtained in 40% yield, m.p. 228-230 °C (ethanol); IR (KBr): ν_{max} 3.80 (s, 3H, $NMe_{quinolone}$), 7.35-7.76 (m, 8H H_{arom}), 8.24 (dd, 1H, C5-$H_{quinolone}$), 8.60 (s, 1H, C5-$H_{pyrazole}$), 10.40 (s, 1H, CH=O), 12.06 (s, 1H, OH) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ_H 3124-2904 (NH, OH), 1678 (CH=O), 1643 (C=$O_{quinolone}$), 1620, 1591; ^{13}C nmr (DMSO-d_6): δ_C 187.9, 160.9, 161.7, 149.1, 138.5 132.3, 130.4, 129.9, 128.2, 124.8, 124.5, 122.1, 119.5, 115.9, 114.1, 101.2, 29.7; MS (EI, 70 eV): *m/z* (*I*%) 345 (76.92) (M^+), 317 (73.48), 300 (3.15), 286 (6.00), 226 (2.29), 77 (100). *Anal.* Calcd. for $C_{20}H_{15}N_3O_3$: C, 69.56; H, 4.38; N, 12.17 %. Found: C, 69.22; H, 4.12; N, 12.00.

General Procedure for the Preparation of the Hydrazones 27a,b. To a stirred solution of the aldehyde **26b** (10 mmol), in ethanol (20 mL), was added 10 mmol of each of hydrazine hydrate (98%) and/or thiosemicarbazide, at room temperature. The mixture was stirred for 3 h and the precipitate so formed was filtered off and crystallized from the proper solvent.

3-(4-Hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde Hydrazone (27a). This compound was obtained in 80% yield, m.p. 216-218 °C (ethanol-water, 5:1); IR (KBr): ν_{max} 3430-3215 (OH, NH_2), 1636 (C=$O_{quinolone}$), 1618, 1570, 1558 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ_H 3.58 (s, 3H, $NMe_{quinolone}$), 7.11-7.60 (m, 11H, H_{arom}), 6.78 (b, 2H, NH_2), 7.87 (d, 2H, H_{arom}), 8.04 (d, 1H, C5-$H_{quinolone}$), 8.59 (s, 1H, C5'-$H_{pyrazole}$), 8.97 (s, 1H, CH=N), 11.92 (b, 1H, OH). *Anal.* Calcd. for $C_{20}H_{17}N_3O_2$: C, 72.49; H, 5.17; N, 12.68 %. Found: C, 72.18; H, 5.01; N, 12.45.

3-(4-Hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde Phenylhydrazone (27b). This compound was obtained in 70% yield, m.p. 260-262 °C (pyridine); IR (KBr): ν_{max} 3430-3157 (NH_2, NH, OH), 1645 (C=$O_{quinolone}$), 1610, 1591, 1358,1232 (N-C=S) cm^{-1}; MS (EI, 70 eV): *m/z* (*I*%) 418 (7.46) (M^+), 342(12.20), 325 (9.32), 326 (43.92), 77 (100). *Anal.* Calcd. for $C_{21}H_{18}N_6O_2S$: C, 60.27; H, 4.34; N, 20.08 %. Found: C, 60.01; H, 4.08; N, 19.76.

6-Methyl-16-phenyl-16*H*-pyrazolo[3',4':4,5]pyrano[3,2-*c*]-quinoline-7,12(6*H*)-dione (29). To a mixture of the aldehyde **26b** (10 mmol) and hydroxylamine hydrochloride (10 mol) in glacial acetic acid (25 mL). The reaction mixture was heated under reflux for 6 h, and then the solution was left to cool at room temperature and poured onto crushed ice. The solid so obtained was filtered, dried, and crystallized from acetic acid, in 75% yield, m.p. 183-184 °C; IR (KBr): ν_{max} 1764 (C=$O_{\alpha\text{-pyrone}}$), 645 (C=$O_{quinolone}$), 1608 (C=N), and 1105 (C-O-C) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ_H 3.68 (s, 3H, N-Me), 7.12-7.76 (m, 8H, Harom), 8.04 (d, 1H, C5-$H_{quinolone}$), 8.62 (s, 1H, C5'$H_{pyrazole}$); MS (EI, 70 eV): *m/z* (*I*%) 343 (100) (M^+), 315 (5.55), 314 (13.05), 299 (1.52), 157 (22.89), 104 (21.04), 77 (99.89). *Anal.* Calcd. for $C_{20}H_{13}N_3O_3$: C, 69.97; H, 3.82; N, 12.24 %. Found: C, 69.77; H, 3.52; N, 12.03.

4-Hydroxy-3-{[(3-(4-hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)-1-phenyl-1*H*-pyrazol-4-yl)methylene]-5-oxo-4,5-dihydro-1*H*-pyrazol-3-yl}-1-methylquinolin-2(1*H*)-one (31). A mixture of the aldehyde **26b** (10 mmol), the pyrazolinone **30** [13] (10 mmol), and anhydrous sodium acetate (15 mmol), in glacial acetic acid (20 mL), was refluxed for 4 h and then poured into ice-cold water. The resulting solid precipitate was collected by filtration and crystallized from acetic acid, in 75% yield, m.p. >300 °C; IR (KBr): ν_{max} 3400-2800 (H-bonded OH, NH), 1648(C=$O_{quinolone}$), 1620 (C=N), 1580-1550 (C=C) cm^{-1}; MS (EI, 70 eV): *m/z* (*I*%) 584 (100) (M^+), 343 (33.40), 317 (64.89), 175 (8.40), 143 (10.56), 77 (100) ($C_6H_5^+$). *Anal.* Calcd. for $C_{33}H_{24}N_6O_5$: C, 67.80; H, 4.14; N, 14.38 %. Found: C, 67.55; H, 3.80; N, 14.05.

4-Hydroxy-1-methyl-3-[(2*E*)-3-[3-(4-hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)1-phenyl-1*H*-pyrazol-4-yl]prop-2-enoyl]quinolin-2(1*H*)-one (32). To a mixture of the acetylquinolinone **1** (10 mmol) and the aldehyde **26b** (10 mmol) a few drops of piperidine was added and the mixture was heated at 100 °C for 3 h. The pasty product obtained was then triturated with methanol (20 mL) and the formed solid material was collected by filtration, washed with diethyl ether, purified by flash-chromatography using ethyl acetate/petroleum ether as eluent (1:2, v/v), and then crystallized from DMF, in 70% yield, m.p. 288-290 °C; IR (KBr): ν_{max} 3315-3200 (broad H-bonded OH), 1650 (C=O), 1633 (C=O), 1620 (C=N), 1557, 1505, 1456, 1425 cm^{-1}; MS (EI, 70 eV): *m/z* (*I*%) 544 (31.10) (M^+), 175 (73.64) ($C_{10}H_9NO_2^+$), 146 (28.05), 134 (54.70), 104 (52.24) (CH_2=$NC_6H_4^+$), 77 (100) ($C_6H_5^+$). *Anal.* Calcd. for $C_{32}H_{24}N_4O_5$: C, 70.58; H, 4.44; N, 10.29 %. Found: C, 70.32; H, 4.11; N, 10.00.

4-Hydroxy-3-{5-[3-(4-hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)-1-phenyl-1*H*-pyrazol-4-yl]-4,5-dihydro-1*H*-pyrazol-3-yl}-1-methylquinolin-2(1*H*)-one (33). A mixture of the compound **32** (10 mmol) and hydrazine hydrate (12 mmol), in absolute ethanol (20 mL) was heated under reflux for 2 h. The reaction mixture was then cooled and poured into cold-water. The solid obtained was collected by filtration, dried and crystallized from ethanol, in 58% yield, m.p. >300 °C; IR (KBr): ν_{max} 3340-3120 (br, NH), 2800-2650 (br, H-bonded OH), 1645 (C=O), 1631 (C=O), 1612 (C=N), 1585, 1550, 1501, 1442, 1426 cm^{-1}; MS (EI, 70 eV): *m/z* (*I*%) 558 (6.81) (M^+), 202 (3.16) ($C_{11}H_{10}N_2O_2^+$), 175 (100) ($C_{10}H_9NO_2^+$), 146 (40.74), 134 (21.43), 105 (42.15) ($C_6H_5C{\equiv}O^+$). *Anal.* Calcd. for $C_{32}H_{26}N_6O_4$: C, 68.81; H, 4.69; N, 15.04 %. Found: C, 68.49; H, 4.50; N, 14.85.

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