HETEROCYCLES, Vol. 87, No. 2, 2013, pp. 369 - 380. © 2013 The Japan Institute of Heterocyclic Chemistry
Received, 26th November, 2012, Accepted, 6th December, 2012, Published online, 20th December, 2012
DOI: 10.3987/COM-12-12639

SYNTHESIS OF SOME NOVEL BINUCLEAR HETEROCYCLIC COMPOUNDS FROM 6-ETHYL-3-NITROPYRANO [3,2-*c*]-QUINOLINE-4,5(6*H*)-DIONE

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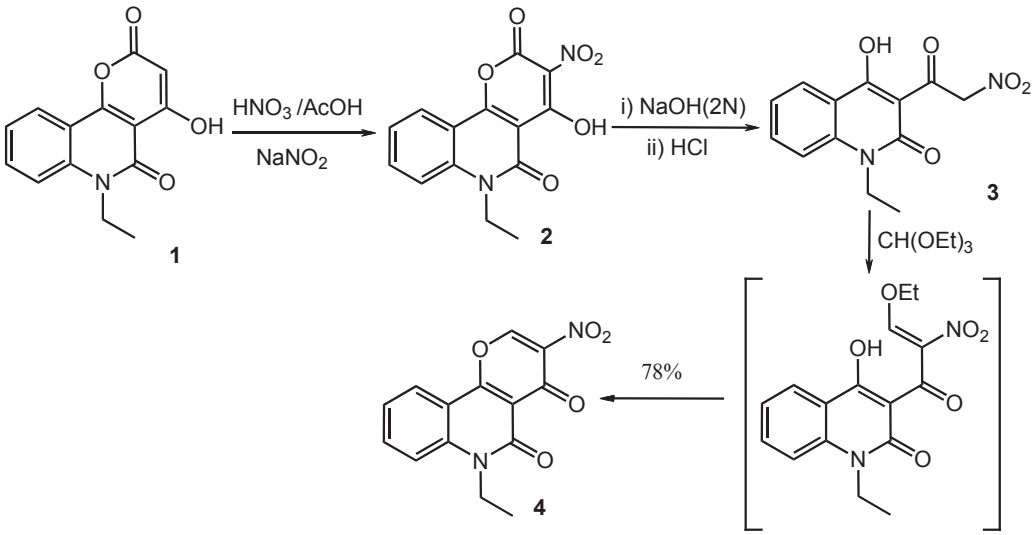
Abstract – 6-Ethyl-3-nitropyrano[3,2-*c*]quinoline-4,5(6*H*)-dione (**4**) was synthesized and its reactivity towards some 1,2-, 1,3-, and 1,4-binucleophiles was investigated. Ring transformation *via* opening of the γ-pyrone ring and heterocyclizations through out these reactions led to certain interesting five, six, and seven-membered heterocyclic substituents, *viz*. pyrazolyl, pyridyl, pyrimidyl, diazepinyl, and thiazepinyl at position-3 of quinolin-2-one moiety.

INTRODUCTION

3-Substituted γ-pyrones are used as valuable synthetic intermediates in the preparation of pharmacologically relevant products and new heterocyclic systems.[1-7] Introduction of a nitro group into the 3-position of γ-pyrone system enhances the reactivity of the pyrone ring towards binucleophilic reagents and provides a broad synthetic potential of nitrogen containing heterocycles.[8] However, 3-nitro-γ-pyrones have not received much attention despite their potential interest as building blocks in synthesis of heterocyclic compounds bearing a nitro group. The chemistry of nucleophilic reactions, involving ring-opening/ring-closing (RORC) of nitropyrano[3,2-*c*]quinoline-4,5-dione, attracted our attention due to the expected higher reactivity of the pyrone ring in presence of nitro group and to the paucity of their literature reports.[8,9] On the other hand, the combination of a pyrazole, pyridine, pyrimidine, and/or diazepine nucleii with the quinoline moiety in one molecular framework is reported to confer interesting biological activity.[10-14] Herein we report the synthesis of the novel 6-ethyl-3-nitropyrano[3,2-*c*]quinoline-4,5(6*H*)-dione (**4**) and study of its chemical behavior towards different binucleophiles to obtain a new series nitroheterocyclyl quinolinone derivatives with the possibility of possessing certain activity.

RESULTS AND DISCUSSION

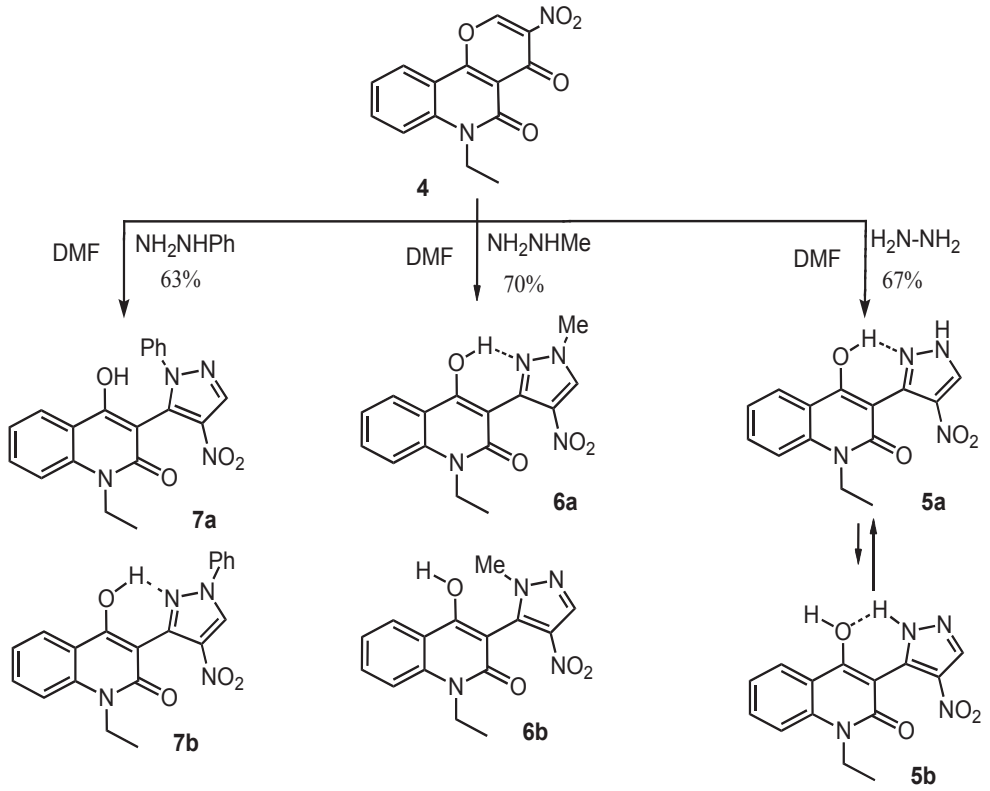
Heating *N*-ethylaniline with two equivalents of diethyl malonate gave 4-hydroxypyrano[3,2-*c*]-quinoline-2,5(6*H*)-dione (**1**).[15,16] Nitration of compound **1** by using conc. nitric acid, in acetic acid, in the presence of sodium nitrite as catalyst, gave nitropyrano[3,2-*c*]quinoline-2,5-dione **2**[17] (Scheme 1). Alkaline hydrolysis of compound **2** using aqueous sodium hydroxide solution yielded the 3-(nitroacetyl)-4-hydroxyquinolinone **3**.[18] Thermal cyclocondensation of the compound **3** with triethyl orthoformate was carried out to get the desired 3-nitropyrano[3,2-*c*]quinoline-4,5-dione **4** (Scheme 1). The IR spectrum of compound **4** confirmed the absence of the hydroxy group. The ^{1}H NMR spectrum of compound **4** showed a new characteristic singlet signal at 8.97 ppm assigned to characteristic C2-H of γ-pyranone. Moreover, the mass spectrum revealed the molecular ion peak [M^+] at *m/z* 286 as the base peak.



Scheme 1

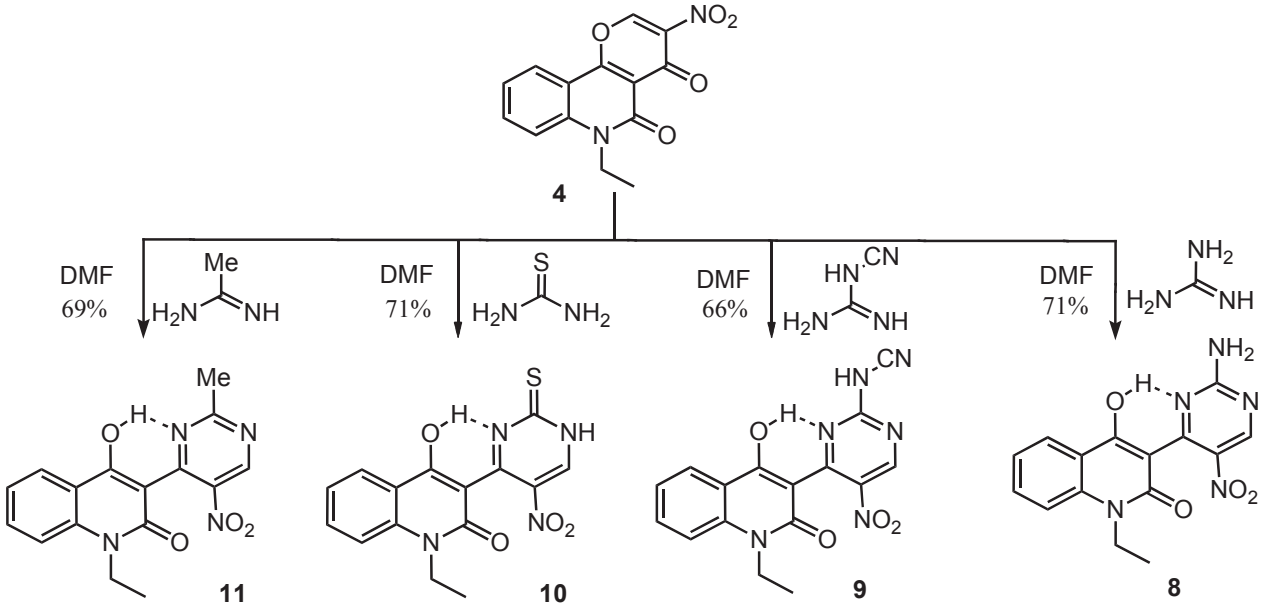
The structural features of the 3-nitro-γ-pyranone **4** show that this molecule possesses two electron-deficient centers (electrophilic sites) at C-2 and C-4, which is activated by strong electron withdrawing nitro- group. The electrophilic sites at position 2 and 4 were utilized for aromatic ring formation by *Michael-type* addition followed by intramolecular cyclocondensation. Reaction of γ-pyrones with hydrazine derivatives was previously reported,[19,20] thus compound **4** was subjected to react with hydrazine hydrate, under reflux in DMF, to afford 3-nitropyrazolylquinolinone **5** (Scheme 2). The ^{1}H NMR spectrum of compound **5,** in a DMSO-d_6 solution, showed two sets of signals due to the possibility of annular prototropy of the pyrazole ring. It is well known that annular tautomerism in NH azoles is a very fast process in the NMR time scale.[21] However, in our case, four signals exhibiting broadening at higher frequency values were observed, indicating that pyrazole **5** exists as a mixture of tautomers **5a** and

5b (65:35). The structural assignments were based on the signals due to the NH and OH protons at 11.22 ppm for NH, 12.94 ppm for OH (tautomer **5a**) and 11.01 ppm for NH, 12.64 ppm for OH (tautomer **5b**). This case is very similar to those of some reported pyrazols prepared from γ-pyranone.[21,22] The structure **5a** is the more abundant tautomer (65%) since its intramolecular O–H……N=C hydrogen bond is stronger than the intramolecular N–H……O–C hydrogen bond in tautomer **5b**, hence gains more stability. Reaction of compound **4** with methylhydrazine, in DMF, afforded 3-(1-methyl-4-nitropyrazolyl) quinolinone **6.** The ^{1}H-NMR spectrum of compound **6** revealed that the isomer **6a** was obtained excluding the presence of the other possible isomer **6b** in which the OH chemical shift appears at 12.59 ppm indicating existence of OH……N intramolecular H -bonding which is not possible in isomer **6b** (Scheme 2). The *N*-methyl protons were observed at 3.81 ppm in its NMR spectrum, while its methyl carbon atom appeared at 20.5 ppm. Treatment of compound **4** with phenylhydrazine afforded the pyrazole **7** (Scheme 2). Mass spectrum of compound **7** showed a peak at 376 assigned to molecular ion peak. While, its ^{1}H-NMR spectrum showed ten aromatic protons, in addition to a characteristic exchangeable singlet signal at 13.68 ppm due to the OH proton. This result confirms absence of intramolecular H-bonding in the product which is in agreement with the structure of isomer **7a.** However, this contrast between behavior of methylhydrazine and phenylhydrazine towards the pyranoquinolinedione **4** can be understood by assuming that the most reactive nucleophilic site attacks the most reactive electrophilic site in the reactant molecule.



Scheme 2

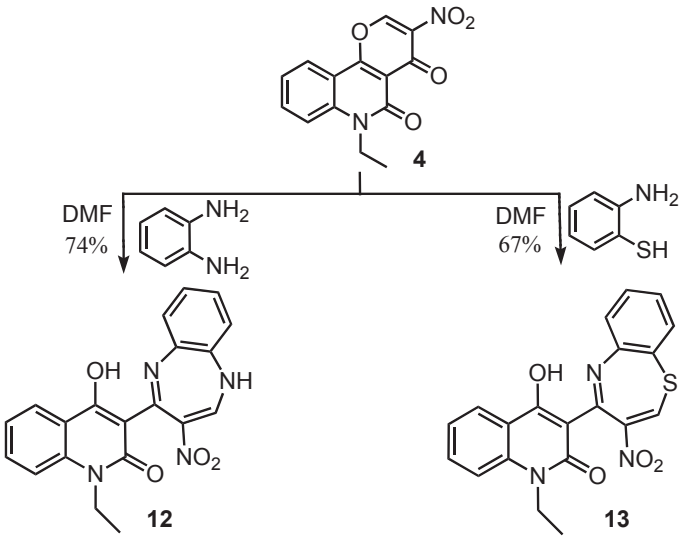
Reaction of γ-pyrones with guanidine derivatives was previously reported.[23] Thus, the compound **4** was allowed to react with some 1,3-binucleophilic reagents in order to prepare 4-hydroxyquinolinones bearing pyrimidine moiety. Treatment of compound **4** with guanidine hydrochloride, in boiling DMF, caused γ-pyrone ring-opening followed by ring-closing (RORC) with loss of H_2O, to give the pyrimidylquinolinone **8** (Scheme 3). The ^{1}H NMR spectrum of the compound **8** showed two broad signals due to three exchangeable protons characteristic for NH_2 and OH at 6.84 and 12.51 ppm. Also, the structure of compound **8** was supported by its mass spectrum which exhibited the molecular ion peak at *m*/*z* 327. Reaction of compound **4** with cyanoguanidine afforded the cyanoamino-pyrimidine derivative **9** (Scheme 3). The IR spectrum of the compound **9** showed the presence of absorption bands at 3120 and 2230 cm^{-1}, characteristic for the NH and C≡N groups, respectively. Furthermore, the ^{1}H NMR spectrum of compound **9** showed two deuterium-exchangeable singlet signals assignable to the NH and the OH protons at δ 8.97, 12.59. The reaction of the compound **4** with thiourea, in DMF, afforded the thioxo-pyrimidine derivative **10** (Scheme 3). The elemental analysis of the product revealed correction of the proposed formulae, in addition to, ^{1}H NMR spectrum of the product **10** showed two deuterium-exchangeable singlet signals at δ 11.99 and 12.63 assignable to NH and OH protons. The reaction of the compound **4** with acetamidine, in DMF, afforded the methylpyrimidine derivative **11** (Scheme 3). ^{1}H NMR spectrum of compound **11** showed a methyl signal as singlet at δ 2.88. This methyl was observed at δ 20.5 in the ^{13}C NMR spectrum.



Scheme 3

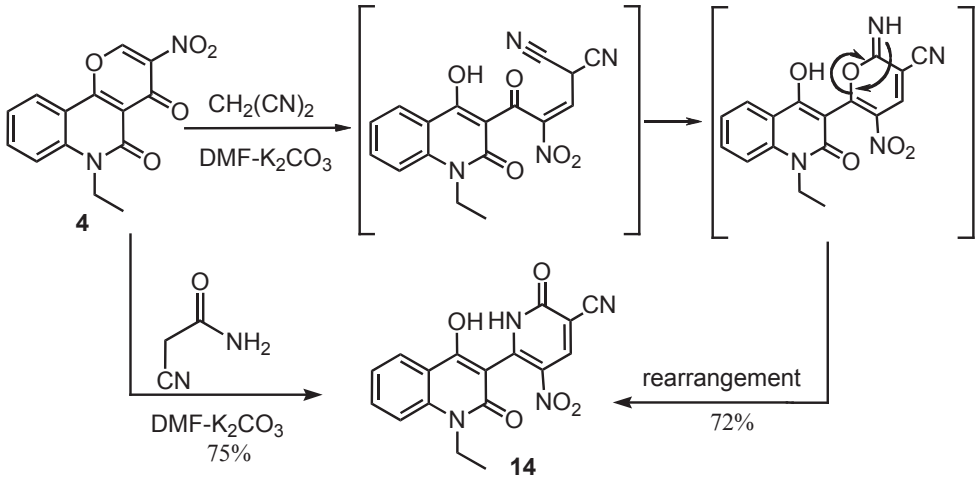
In continuation to this study, the reactivity of the compound **4** towards 1,4-binucleophiles, such as *o*-phenylendiamine and *o*-aminothiophenol was investigated. The reaction was carried out in boiling DMF giving rise to the corresponding benzodiazepines **12**, **13**. The anticipated structure of the 1,5-benzodiazepine **12** and 1,5-benzothiazepine **13** was established on basis of elemental microanalysis,

and spectral data. ^{1}H NMR spectra of both products **12** and **13** revealed that the integral count of protons in the aromatic region is corresponding to nine protons of two benzo groups in addition to 2-CH of diazepine.



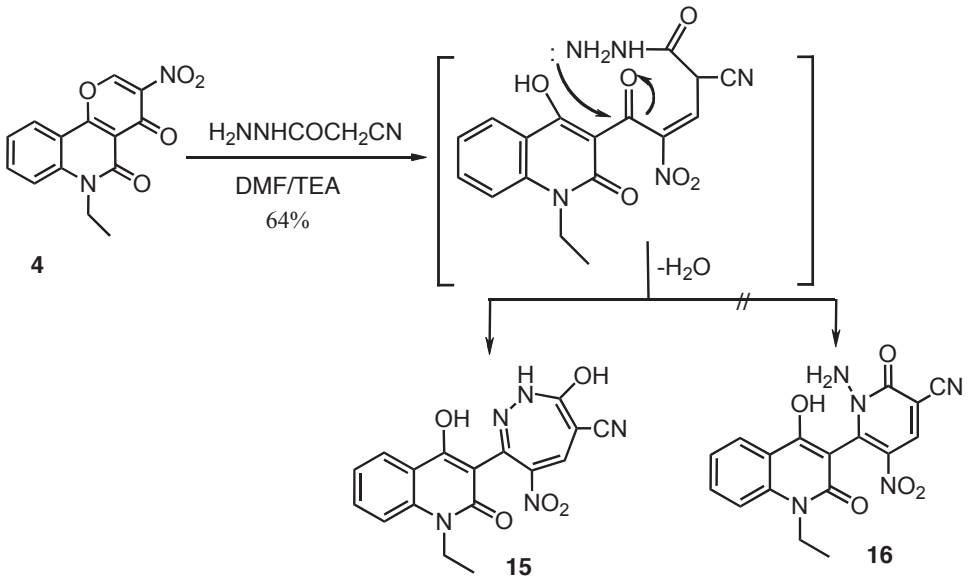
Scheme 4

Reaction of the γ-pyrones with carbon nucleophiles was previously studied.[24] Thus, treatment of the compound **4** with malononitrile, in DMF containing anhydrous potassium carbonate, gave 3-pyridinylquinolinone derivative **14** (Scheme 5). The same compound **14** was obtained from reaction of the compound **4** with cyanoacetamide under the same conditions (Scheme 5). The IR spectrum of compound **14** showed absorption bands at 3446, 3230 and 2245 cm^{-1} assigned to OH, NH and C≡N groups, respectively. ^{1}H NMR spectrum of the compound **14** revealed two broad signals at 10.51 ppm and 12.93 ppm for the NH and OH protons exchangeable with D_2O.



Scheme 5

Reaction of the compound **4** with cyanoacetohydrazide as a 1,4-*C,N*-dinucleophile was carried out, in refluxing DMF containing catalytic amount of triethyl amine. Compound **15** was obtained, while the other possible product *N*-aminopyridine derivative **16** was not observed (Scheme **6**). The ^{1}H NMR spectrum of compound **15** revealed three different broad signals exchangeable with D_2O at 10.89, 11.01 and 12.94 ppm corresponding to one NH and two OH protons. There is no indication for presence of NH_2 group characteristic chemical shift signal. These observations fortify the suggested structure of compound **15**.



Scheme 6

EXPERIMENTAL

Melting points were determined on a digital Stuart SMP3 apparatus. Infrared spectra were measured on Perkin-Elmer 293 spectrophotometer (cm^{-1}), using KBr disks. ^{1}H NMR spectra were measured on Gemini-200 spectrometer (200 MHz), Mercury-300BB (300MHz), and/or Jeol Eca-500 MHz using DMSO-d_6 as a solvent and TMS (δ) as the internal standard. ^{13}C NMR spectra were measured on Mercury-300BB (75 MHz), using DMSO-d_6 as a solvent and TMS (δ) as the internal standard. Mass spectra were obtained using GC-2010 Shimadzu Gas chromatography instrument mass spectrometer (70 eV). Elemental microanalyses were performed on a Perkin–Elmer CHN-2400 analyzer.

6-Ethyl-3-nitropyrano[3,2-*c*]quinoline-4,5(6*H*)-dione (4)

A mixture of compound **3** (2.76 g, 10 mmol) and triethyl orthoformate (4 mL, 25 mmol), was heated under fusion condition for 4 h. The solid deposited during heating was filtered, air dried and crystallized from AcOH to give compound **4** as yellow crystals, mp > 300 ºC, yield (2.23 g, 78%). IR (KBr, cm^{-1}): 3072 (CH_{arom}), 2977, 2928, 2866 (CH_{aliph}), 1674 ($C{=}O_{pyrone}$), 1633 ($C{=}O_{quinolone}$), 1591 (C=C), 1568, 1377 (NO_2). ^{1}H NMR (DMSO-d_6, δ): 1.22 (t, 3H, J = 6.9 Hz, CH_2CH_3), 4.35 (q, 2H, J = 6.9 Hz, CH_2CH_3), 7.45 (t, 1H, J = 7.2 Hz, H-9), 7.78 (d, 1H, J = 8.4 Hz, H-7), 7.92 (t, 1H, J = 7.2 Hz, H-8), 8.14 (d, 1H, J = 8.1

Hz, H-10), 8.97 (s, 1H, H-2). ^{13}C NMR (125 MHz, DMSO-d_6, δ): 11.8 (CH_3), 37.4 (CH_2), 111.9, 115.9, 123.4, 124.5, 132.1, 132.3, 135.8, 140.3, 140.9, 161.1, 162.0, 174.6. M/z (relative intensity): 287 [M^+ +1; 17], 286 [M^+; 100], 285 [M^+-1; 48], 258 (42), 225 (12), 214 (24), 200 (10), 184 (29), 169 (17), 156 (67), 154 (10), 146 (67), 141 (18), 140 (11), 132 (37), 129 (12), 128 (36), 127 (20), 118 (14), 115 (12), 114 (22), 113 (11), 105 (12), 104 (20), 102 (13), 101 (31), 91 (13), 90 (13), 89 (10), 77 (55), 76 (23). Anal. Calcd for $C_{14}H_{10}N_2O_5$ (286.25): C, 58.75; H, 3.52; N, 9.79. Found C, 58.31; H, 3.49; N, 9.61%.

General procedure for formation of the 3-pyrazolylquinolines 5-7

A mixture of γ-pyrone **4** (2.86 g, 10 mmol) and some hydrazines namely; hydrazine hydrate (0.6 mL, 12 mmol), methylhydrazine (0.64 mL, 12 mmol), phenylhydrazine (1.2 mL, 12 mmol), in DMF (50 mL), was heated under reflux for 4 h. After partial evaporation of the solvent the product was isolated by filtration, washed with EtOH, dried and crystallized from the proper solvent to give the compounds **5**, **6** and **7** respectively.

1-Ethyl-4-hydroxy-3-(4-nitro-1*H*-pyrazol-3-yl)quinolin-2(1*H*)-one (5)

Crystallized from DMF to give compound **5** as pale yellow crystals, mp > 300 ºC, yield (2.01 g, 67%). IR (KBr, cm^{-1}): 3447-3150 (OH, NH), 3055 (CH_{arom}), 2981 (CH_{aliph}), 1655 ($C{=}O_{quinolone}$), 1601 (C=N), 1591 (C=C), 1558, 1376 (NO_2). ^{1}H NMR (300 MHz, DMSO-d_6, δ): (**5a**, OH…….N, 65%) 1.28 (t, 3H, J = 6.4 Hz, CH_2CH_3), 4.38 (q, 2H, J = 6.4 Hz, CH_2CH_3), 7.37 (t, 1H, J = 7.4 Hz, H-6), 7.61 (d, 1H, J = 8.2 Hz, H-8), 7.71 (t, 1H, J = 7.4 Hz, H-7), 7.96 (s, 1H, $H_{pyrazole}$), 8.12 (d, 1H, J = 8.0 Hz, H-5), 11.22 (s, 1H, NH exchangeable with D_2O), 12.94 (s, 1H, OH exchangeable with D_2O); (**5b**, NH…….O, 35%) 1.20 (t, 3H, J = 6.9 Hz, CH_2CH_3), 4.18 (q, 2H, J = 6.9 Hz, CH_2CH_3), 7.19 (t, 1H, J = 7.2 Hz, H-6), 7.50 (d, 1H, J = 8.0 Hz, H-8), 7.59 (t, 1H, J = 7.2 Hz, H-7), 7.84 (s, 1H, $H_{pyrazole}$), 8.06 (d, 1H, J = 7.9 Hz, H-5), 11.01 (s, 1H, NH exchangeable with D_2O), 12.64 (s, 1H, OH exchangeable with D_2O). M/z (relative intensity): 301 [M^+ +1; 5], 300 [M^+; 17], 299 [M^+-1; 57], 280 (12), 279 (92), 270 (20), 242 (19), 228 (22), 189 (36), 188 (38), 146 (100), 132 (60), 130 (74), 120 (39), 104 (30), 90 (27). Anal. Calcd for $C_{14}H_{12}N_4O_4$ (300.28): C, 56.00; H, 4.03; N, 18.66. Found C, 55.91; H, 4.01; N, 18.31%.

1-Ethyl-4-hydroxy-3-(1-methyl-4-nitro-1*H*-pyrazol-3-yl)quinolin-2(1*H*)-one (6)

Crystallized from AcOH to give **6** as colorless crystals, mp 286-287 ºC, yield (2.19 g, 70%). IR (KBr, cm^{-1}): 3443 (OH), 3075 (CH_{arom}), 2979, 2930, 2867 (CH_{aliph}), 1630 ($C{=}O_{quinolone}$), 1603 (C=N), 1595 (C=C), 1551, 1378 (NO_2). ^{1}H NMR (300 MHz, DMSO-d_6, δ): 1.22 (t, 3H, J = 6.6 Hz, CH_2CH_3), 3.81 (s, 3H, NCH_3), 4.35 (q, 2H, J = 6.6 Hz, CH_2CH_3), 7.30 (t, 1H, J = 7.2 Hz, H-6), 7.63-7.67 (m, 2H, J = 8.0 Hz, H-8 and H-7), 7.99 (s, 1H, $H_{pyrazole}$), 8.01 (d, 1H, J = 7.8 Hz, H-5), 12.59 (s, 1H, OH exchangeable with D_2O). ^{13}C NMR (125 MHz, DMSO-d_6, δ): 12.8 (CH_3), 20.5 (NCH_3), 37.5 (CH_2), 98.8, 108.3, 112.8, 114.9, 116.6, 122.5, 123.4, 131.3, 136.6, 138.2, 159.4, 164.6. Anal. Calcd for $C_{15}H_{14}N_4O_4$ (314.30): C, 57.32; H, 4.46; N, 17.83%. Found C, 57.31; H, 4.42; N, 17.81%.

1-Ethyl-4-hydroxy-3-(4-nitro-1-phenyl-1*H*-pyrazol-5-yl)quinolin-2(1*H*)-one (7)

Crystallized from AcOH to give **7** as yellow crystals, mp > 300 ºC, yield (2.36 g, 63%). IR (KBr, cm^{-1}): 3447 (OH), 3078 (CH_{arom}), 2979, 2930 (CH_{aliph}), 1630 ($C=O_{quinolone}$), 1603 (C=C), 1551, 1378 (NO_2). ^1H NMR (DMSO, δ): 1.18 (t, 3H, *J* = 6.0 Hz, CH_2CH_3), 4.28 (q, 2H, *J* = 7.2 Hz, CH_2CH_3), 7.19 (t, 1H, *J* = 6.4 Hz, Ar-H), 7.30 (d, 1H, *J* = 6.8 Hz, Ar-H), 7.46 (d, 1H, *J* = 6.0 Hz, Ar-H), 7.60 – 7.79 (m, 5H, Ar-H), 8.03 (s, 1H, $H_{pyrazole}$), 8.23 (d, 1H, *J* = 6.9 Hz, H-5), 13.68 (s, 1H, OH exchangeable with D_2O). M/z (relative intensity): 377 [M^+ +1; 27], 376 [M^+; 45], 359 (47), 357 (57), 342 (54), 333 (55), 326 (52), 310 (60), 305 (51), 288 (57), 279 (56), 269 (90), 258 (46), 241 (75), 227 (58), 209 (50), 189 (100), 174 (86), 132 (94), 105 (83), 77 (67). Anal. Calcd for $C_{20}H_{16}N_4O_4$ (376.37): C, 63.83; H, 4.26; N, 14.89%. Found C, 63.31; H, 4.24; N, 14.87%.

General procedure for formation of the 3-pyrimidylquinolines 8-11

A mixture of γ-pyrone **4** (2.86 g, 10 mmol) and 1,3-binuchleophiles namely; guanidine hydrochloride (0.96 g, 10 mmol), cyanoguanidine (0.84 g, 10 mmol), thiourea (0.76 g, 10 mmol), acetamidine hydrochloride (0.95 g, 10 mmol), in DMF (50 mL), was heated under reflux for 4 h. The solid deposited after cooling was filtered and crystallized from the proper solvent to give the compounds **8**, **9**, **10** and **11**, respectively.

1-Ethyl-3-(2-amino-5-nitropyrimidin-4-yl)-4-hydroxyquinolin-2(1*H*)-one (8)

Crystallized from DMF to give **8** as colorless crystals, mp > 300 ºC, yield (2.32 g, 71%). IR (KBr, cm^{-1}): 3420 (OH), 3316, 3234 (NH_2), 3070 (CH_{arom}), 2977, 2934 (CH_{aliph}), 1634 ($C=O_{quinolone}$), 1610 (C=N), 1591 (C=C), 1568, 1376 (NO_2). ^1H NMR (300 MHz, DMSO-d_6, δ): 1.26 (t, 3H, *J* = 6.6 Hz, CH_2CH_3), 4.38 (q, 2H, *J* = 6.6 Hz, CH_2CH_3), 6.84 (bs, 2H, NH_2 exchangeable with D_2O), 7.33 (t, 1H, *J* = 7.2 Hz, H-6), 7.66-7.70 (m, 2H, H-8 and H-7), 7.96 (s, 1H, $H_{pyrimidine}$), 8.08 (d, 1H, *J* = 8.4 Hz, H-5), 12.51 (s, 1H, OH exchangeable with D_2O). *m/z* (relative intensity): 328 [M+ +1; 5], 327 [M+; 8], 311 (5), 256 (7), 228 (7), 213 (15), 204 (6), 194 (7), 185 (13), 169 (8), 149 (32), 137 (9), 129 (19), 121 (10), 115 (12), 109 (13), 98 (34), 81 (79), 73 (66), 69 (100). Anal. Calcd for $C_{15}H_{13}N_5O_4$ (327.30): C, 55.05; H, 4.00; N, 21.40%. Found C, 55.02; H, 3.97; N, 21.36%.

4-(1-Ethyl-1,2-dihydro-4-hydroxy-2-oxoquinolin-3-yl)-5-nitropyrimidin-2-ylcyanamide (9)

Crystallized from DMF to give **9** as colorless crystals, mp > 300 ºC, yield (2.32 g, 66%). IR (KBr, cm^{-1}): 3416 (OH), 3120 (NH), 3055 (CH_{arom}), 2984, 2881 (CH_{aliph}), 2230 (CN), 1646 (C=O), 1615 (C=N), 1595 (C=C), 1558, 1365 (NO_2). ^1H NMR (DMSO, δ): 1.20 (t, 3H, *J* = 7.0 Hz, CH_2CH_3), 4.33 (q, 2H, *J* = 7.2 Hz, CH_2CH_3), 7.33 (t, 1H, *J* = 6.4 Hz, H6), 7.58 - 7.71 (m, 2H, H8 and H7), 7.99 (s, 1H, $H_{pyrimidine}$), 8.11 (d, 1H, *J* = 6.9 Hz, H-5), 8.97 (bs, 1H, NH exchangeable with D_2O), 12.59 (s, 1H, OH exchangeable with D_2O). M/z (relative intensity): 352 [M^+; 40], 351 [M^+-1; 52], 331 (56), 313 (46), 304 (50), 285 (68), 267 (58), 251 (53), 235 (50), 192 (52), 188 (92), 167 (63), 161 (86), 146 (74), 130 (100), 125 (58), 104

(68), 90 (92), 82 (58), 71 (56). Anal. Calcd for $C_{16}H_{12}N_6O_4$ (352.31): C, 54.55; H, 3.43; N, 23.85%. Found C, 54.73; H, 3.41; N, 23.43%.

1-Ethyl-3-(1,2-dihydro-5-nitro-2-thioxopyrimidin-4-yl)-4-hydroxyquinolin-2(1*H*)-one (10)

Crystallized from AcOH to give **10** as yellow crystals, mp > 300 ºC, yield (2.44 g, 71%). IR (KBr, cm^{-1}): 3393 (OH), 3197 (NH), 3068 (CH_{arom}), 2922, 2870 (CH_{aliph}), 1647 (C=O), 1615 (C=N), 1558, 1370 (NO_2). ^1H NMR (DMSO-d_6, δ): 1.22 (t, 3H, J = 6.9 Hz, CH_2CH_3), 4.38 (q, 2H, J = 6.9 Hz, CH_2CH_3), 7.37 (t, 1H, J = 7.6 Hz, H-6), 7.65–7.76 (m, 2H, H-7 and H-8), 7.99 (s, 1H, $H_{pyrimidine}$), 8.05 (d, 1H, J = 8.4 Hz, H-5), 11.99 (s, 1H, NH exchangeable with D_2O), 12.63 (s, 1H, OH exchangeable with D_2O). M/z (relative intensity): 344 [M^+; 72], 343 [M^+ -1; 77], 323 (95), 320 (75), 293 (91), 252 (81), 245 (79), 236 (76), 218 (75), 182 (85), 156 (79), 128 (75), 119 (65), 101 (72), 62 (72), 52 (100). Anal. Calcd for $C_{15}H_{12}N_4O_4S$ (344.35): C, 52.32; H, 3.51; N, 16.27; S, 9.31%. Found C, 52.13; H, 3.49; N, 16.23; S, 9.21%.

1-Ethyl-4-hydroxy-3-(2-methyl-5-nitropyrimidin-4-yl)quinolin-2(1*H*)-one (11)

Crystallized from DMF to give **11** as colorless crystals, mp 283 - 285 °C, yield (2.24 g, 69%). IR (KBr, cm^{-1}): 3426 (OH), 3068 (CH_{arom}), 2975, 2922 (CH_{aliph}), 1644 (C=O), 1619 (C=N), 1581 (C=C), 1548, 1392 (NO_2). ^1H NMR (DMSO-d_6, δ): 1.26 (t, 3H, J = 6.9 Hz, CH_2CH_3), 2.88 (s, 3H, CH_3), 4.33 (q, 2H, J = 6.9 Hz, CH_2CH_3), 7.47 (t, 1H, J = 7.4 Hz, H-6), 7.58–7.77 (m, 2H, H-7 and H-8), 7.95 (s, 1H, $H_{pyrimidine}$), 8.08 (d, 1H, J = 8.2 Hz, H-5), 12.68 (s, 1H, OH exchangeable with D_2O). ^{13}C NMR (125 MHz, DMSO-d_6, δ): 12.8 (CH_3), 20.5 ($CH_{3\ pyrimidine}$), 37.5 (CH_2), 99.4, 106.8, 108.4, 114.9, 116.7, 122.4, 123.4, 129.2, 131.3, 136.7, 146.5, 159.5, 164.8. Anal. Calcd for $C_{16}H_{14}N_4O_4$ (326.31): C, 58.89; H, 4.32; N, 17.17%. Found C, 58.83; H, 4.31; N, 17.13%.

General procedure for formation of the 3-benzodiazepinylquinolines 12 and 13

A mixture of compound **4** (2.86 g, 10 mmol) and 1,4-binuchleophiles namely; *O*-phenylendiamine (1.1 g, 10 mmol), *O*-aminothiophenol (1.1 mL, 10 mmol), in DMF (50 mL), was heated under reflux for 4 h. The solid deposited after cooling was filtered and crystallized from the proper solvent to give compounds **12** and **13**, respectively.

1-Ethyl-4-hydroxy-3-(3-nitro-1*H*-benzo[*b*][1,4]diazepin-4-yl)quinolin-2(1*H*)-one (12)

Crystallized from AcOH to give **12** as yellow crystals, mp > 300 °C, yield (2.78 g, 74%). IR (KBr, cm^{-1}): 3477 (OH), 3227 (NH), 3055 (CH_{arom}), 2976, 2931 (CH_{aliph}), 1630 (C=O), 1592 (C=C), 1548, 1320 (NO_2). ^1H NMR (DMSO-d_6, δ): 1.24 (t, 3H, J = 6.9 Hz, CH_2CH_3), 4.31 (q, 2H, J = 6.9 Hz, CH_2CH_3), 6.49 - 8.12 (m, 8H, Ar-H), 8.05 (d, 1H, J = 8.4 Hz, H-5), 10.90 (s, 1H, NH exchangeable with D_2O), 13.43 (s, 1H, OH exchangeable with D_2O). ^{13}C NMR (75 MHz, DMSO-d_6, δ): 16.1 (CH_3), 38.6 (CH_2), 98.5, 110.8, 113.7, 117.7, 118.2, 119.4, 119.6, 122.3, 124.2, 124.9, 128.4, 134.6, 135.4, 144.7, 153.7, 155.4, 158.5, 164.1. M/z (relative intensity): 376 [M^+; 15], 375 [M^+ -1; 8], 306 (20), 305 [M^+- O_2N-C≡CH, 100], 304 (40), 326 (23), 310 (19), 290 (30), 277 (84), 250 (32), 230 (23), 223 (32), 197 (30), 188 (60),

172 (44), 161 (58), 146 (43) , 132 (79), 118 (48), 90 (38), 77 (79). Anal. Calcd for $C_{20}H_{16}N_4O_4$ (376.37): C, 63.83; H, 4.28; N, 14.89%. Found C, 63.80; H, 4.19; N, 14.53.

1-Ethyl-4-hydroxy-3-(3-nitrobenzo[*b*][1,4]thiazepin-4-yl)quinolin-2(1*H*)-one (13)

Crystallized from AcOH to give **13** as white crystals, yield (2.63 g, 67%), mp 213 °C. IR (KBr, cm^{-1}): 3416 (OH), 3068 (CH_{arom}), 2922, 2870 (CH_{aliph}), 1646 (C=O), 1615 (C=N), 1595 (C=C), 1558, 1378 (NO_2). ^{1}H NMR (DMSO-d_6, δ): 1.26 (t, 3H, *J* = 6.9 Hz, CH_2CH_3), 4.31 (q, 2H, *J* = 6.9 Hz, CH_2CH_3), 7.19 (t, 1H, *J* = 7.5 Hz, Ar-H), 7.31–7.35 (m, 2H, Ar-H), 7.49 (d, 1H, *J* = 8.2 Hz, Ar-H), 7.65 (t, 1H, *J* = 7.6 Hz, Ar-H), 7.76 -7.79 (m, 2H, Ar-H), 7.97 (s, 1H, $H_{thiazepine}$), 8.21 (d, 1H, *J* = 7.9 Hz, H-5), 13.68 (s, 1H, OH exchangeable with D_2O). M/z (relative intensity): 393 [M^+; 13], 322 [M^+- O_2N-C≡CH, 100], 321 (60), 294 (65), 286 (38), 279 (32), 268 (46), 242 (15), 237 (17), 221 (19), 146 (24), 132 (34), 120 (32), 119 (27), 108 (25), 91 (23), 73 (98). Anal. Calcd for $C_{20}H_{15}N_3O_4S$ (393.42): C, 61.06; H, 3.84; N, 10.68; S, 8.15%. Found C, 61.03; H, 3.78; N, 10.43; S, 8.11%.

1-Ethyl-4-hydroxy-3-(5-nitro-2-oxo-3-cyanopyridin-6-yl)quinolin-2(1*H*)-one (14)

Method A. A mixture of γ-pyrone **4** (2.86 g, 10 mmol) and malononitrile (0.66 g, 10 mmol), in DMF (50 mL) containing small amount of anhydrous potassium carbonate, was heated under reflux for 4 h. The solid deposited after cooling was filtered and crystallized from *i*-PrOH to give compound **14**, as pale brown crystals, mp > 300 °C. yield (2.53 g, 72%). *Method B*. A mixture of γ-pyrone **4** (2.86 g, 10 mmol) and cyanoacetamide (0.84 g, 10 mmol), in DMF (50 mL) containing small amount of anhydrous potassium carbonate, was heated under reflux for 4h. The solid deposited after cooling was filtered and crystallized from *i*-PrOH to give compound **14**, as pale brown crystals, mp > 300 °C. yield (2.64 g, 75%). IR (KBr, cm^{-1}): 3446 (OH), 3230 (NH), 3084 (CH_{arom}), 2977, 2929 (CH_{aliph}), 2245 (CN), 1675 (C= $O_{pyridine}$), 1632 (C= $O_{quinolone}$), 1599 (C=C), 1574, 1384 (NO_2). ^{1}H NMR (300 MHz, DMSO-d_6, δ): 1.16 (t, 3H, *J* = 6.4 Hz, CH_2CH_3), 4.30 (q, 2H, *J* = 6.4 Hz, CH_2CH_3), 7.25 (t, 1H, *J* = 7.2 Hz, H-6), 7.41-7.58 (m, 2H, H-8 and H-7), 7.72 (s, 1H, $H_{pyridine}$), 8.11 (d, 1H, *J* = 8.0 Hz, H-5), 10.51 (s, 1H, NH exchangeable with D_2O), 12.93 (s, 1H, OH exchangeable with D_2O). ^{13}C NMR (125 MHz, DMSO-d_6, δ): 12.9 (CH_3), 35.5 (CH_2), 89.8, 112.9, 114.2, 119.5, 120.8, 121.6, 123.4, 125.8, 129.6, 132.3, 133.5, 139.1, 150.2, 162.2 (C=O), 174.8 (C=O). M/z (relative intensity): 352 [M^+; 40], 351 [M^+-1; 52], 331 (57), 313 (45), 297 (41), 271 (55), 260 (43), 235 (50), 210 (48), 202 (18), 188 (92), 186 (49), 169 (5), 158 (17), 146 (74), 131 (100), 104 (68), 91 (51), 82 (58), 77 (81). Anal. Calcd for $C_{17}H_{12}N_4O_5$ (352.31): C, 57.96; H, 3.43; N, 15.90%. Found C, 57.83; H, 3.36; N, 15.73%.

7-(1-Ethyl-4-hydroxy-2-oxo-1,2-dihydro-quinolin-3-yl)-3-hydroxy-6-nitro-2*H*-[1,2]diazepine-4-carbonitrile (15)

A mixture of compound **4** (2.86 g, 10 mmol) and cyanoacetohydrazide (1 g, 10 mmol), in DMF (50 mL) containing few drops of triethylamine, was refluxed for 4 h. After cooling the solid obtained was filtered

and crystallized from DMF to give **15** as yellow crystals, mp > 300 ºC, yield (2.34 g, 64 %). IR (KBr, cm^{-1}): 3440-3243 (bs, NH and 2OH), 3089 (CH_{arom}), 2978, 2933 (CH_{aliph}), 2234 (C≡N), 1645 ($C=O_{quinolone}$), 1605 (C=C), 1561, 1378 (NO_2). ^{1}H NMR (DMSO-d_6, δ): 1.26 (t, 3H, J = 6.9 Hz, CH_2CH_3), 4.38 (q, 2H, J = 6.9 Hz, CH_2CH_3), 7.34 (t, 1H, J = 7.6 Hz, H-6), 7.59–7.71 (m, 2H, H-7 and H-8), 7.92 (s, 1H, $H_{diazepine}$), 8.12 (d, 1H, J = 8.4 Hz, H-5), 10.89 (s, 1H, NH exchangeable with D_2O), 11.01 (s, 1H, OH exchangeable with D_2O), 12.94 (s, 1H, OH exchangeable with D_2O). ^{13}C NMR (75 MHz, DMSO-d_6, δ): 12.5 (CH_3), 37.4 (CH_2), 98.7, 111.9, 113.8, 115.9, 123.4, 124.5, 132.1, 132.3, 135.8, 140.3, 140.9, 144.7, 153,4, 159.5, 164.6. M/z (relative intensity): 367 [M^+; 25], 366 [M^+-1; 20], 349 (24), 326 (27), 319 (24), 303 (26), 278 (26), 265 (25), 252 (22), 230 (21), 222 (24), 213 (22), 189 (26), 175 (21), 168 (25), 160 (24), 148 (31), 129 (29), 121 (31), 115 (26), 102 (26), 95 (31), 86 (100), 77 (36), 64 (45). Anal. Calcd for $C_{17}H_{13}N_5O_5$ (367.32): C, 55.59; H, 3.57; N, 19.07%. Found C, 55.63; H, 3.69; N, 19.03%.

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