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ORIGINAL PAPER

Facile synthesis of new pyrano[3,2-*c*]quinolones via the reaction of quinolin-2-ones with ethene-1,2,3,4-tetracarbonitrile

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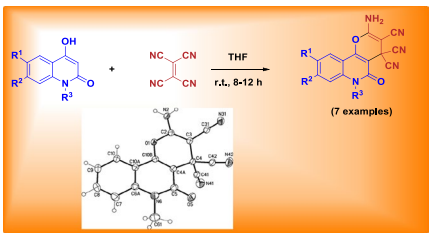
Abstract

Synthesis of heteroannulated pyrano[3,2-*c*]quinolones was established starting from the reaction of 4-hydroxyquinolin-2-ones with ethene-1,2,3,4-tetracarbonitrile. Several conditions were carried out, and the corresponding product yields were illustrated. The neutral and non-polar condition was the best procedure for product formation. The structure of products was elucidated by NMR, IR, mass spectra, and elemental analysis. X-ray structure analysis was also used to elucidate the structure of the obtained products. The mechanism of products formation was also discussed.

Graphical abstract



Keywords Ethene-1,2,3,4-tetracarbonitrile · 4-Hydroxyquinolin-2-ones · Mechanism · Neutral and non-polar condition · X-ray structure analysis

Introduction

Quinoline moieties are important in anticancer drug improvement, as their derivatives show great results through different operations such as growth inhibitors by cell cycle arrest, apoptosis, inhibition of angiogenesis, disruption of cell migration, and modulation of nuclear receptor responsiveness [1]. The fused pyranoquinoline moiety is an extremely common structural motif, existing in many naturally occurring or biologically active alkaloids [2–4]. The natural product Haplamine (Fig. 1), extracted from *Haplophyllum perforatum*, is commonly used in central Asia to treat various diseases, including testicular cancer. Researchers evaluated the haplamine-induced cell death and its major metabolites *trans/cis*-3,4-dihydroxyhaplamine (**1** and **2**, Fig. 1). The IC_{50} values were 52.5, 24.3, 59.7, 41.5, 72, 32 µM in human pancreatic cancer (Capan1 and Capan2),

Dedicated for the memory of Professor Dr. Raafat Mohamed Shaker.

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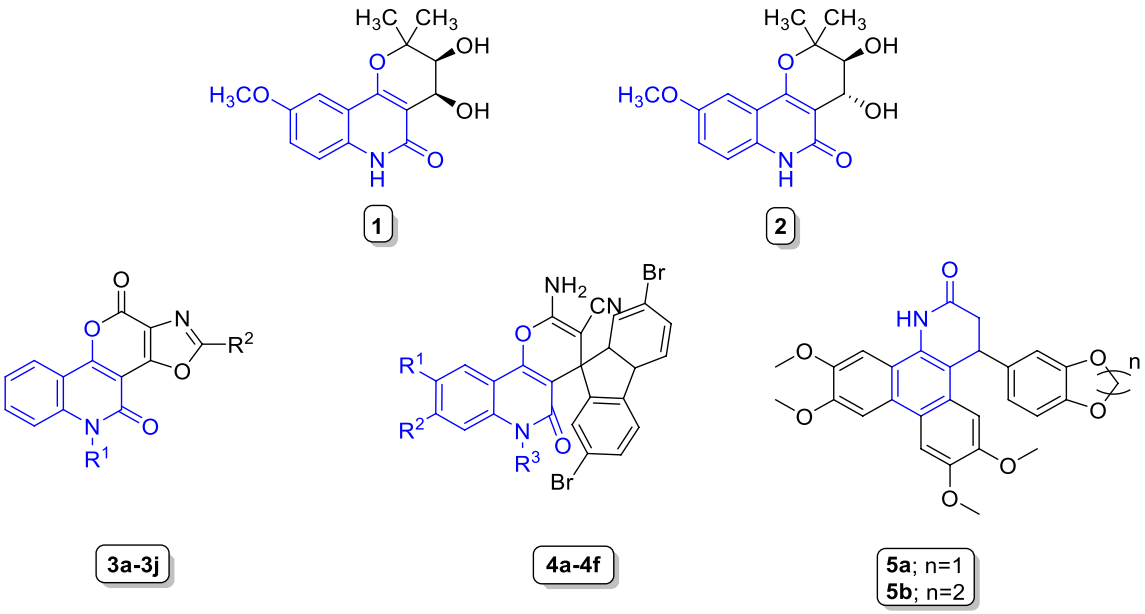


3a: $R^1 = R^2 = CH_3$
b: $R^1 = C_2H_5$, $R^2 = CH_3$
c: R^1 = *n*-Bu, $R^2 = CH_3$
f: R^1 = *n*-Bu, $R^2 = C_2H_5$
h: $R^1 = C_2H_5$, R^2 = *n*-Bu
j: $R^1 = CH_3$, R^2 = *n*-Bu

4a: $R^1 = R^2 = R^3 = H$
4b: R^1 = Cl, $R^2 = R^3 = H$
4c: $R^1 = CH_3$, $R^2 = R^3 = H$
4d: $R^1 = R^3$ =H, $R^2 = CH_3$
4e: R^1 = Br, $R^2 = R^3 = H$
4f: $R^1 = OCH_3$, $R^2 = R^3 = H$

Fig. 1 Structure of anticancer pyranoquinolones **1**, **2**, **3a–3j**, **4a–4f**, and **5a**, **5b**

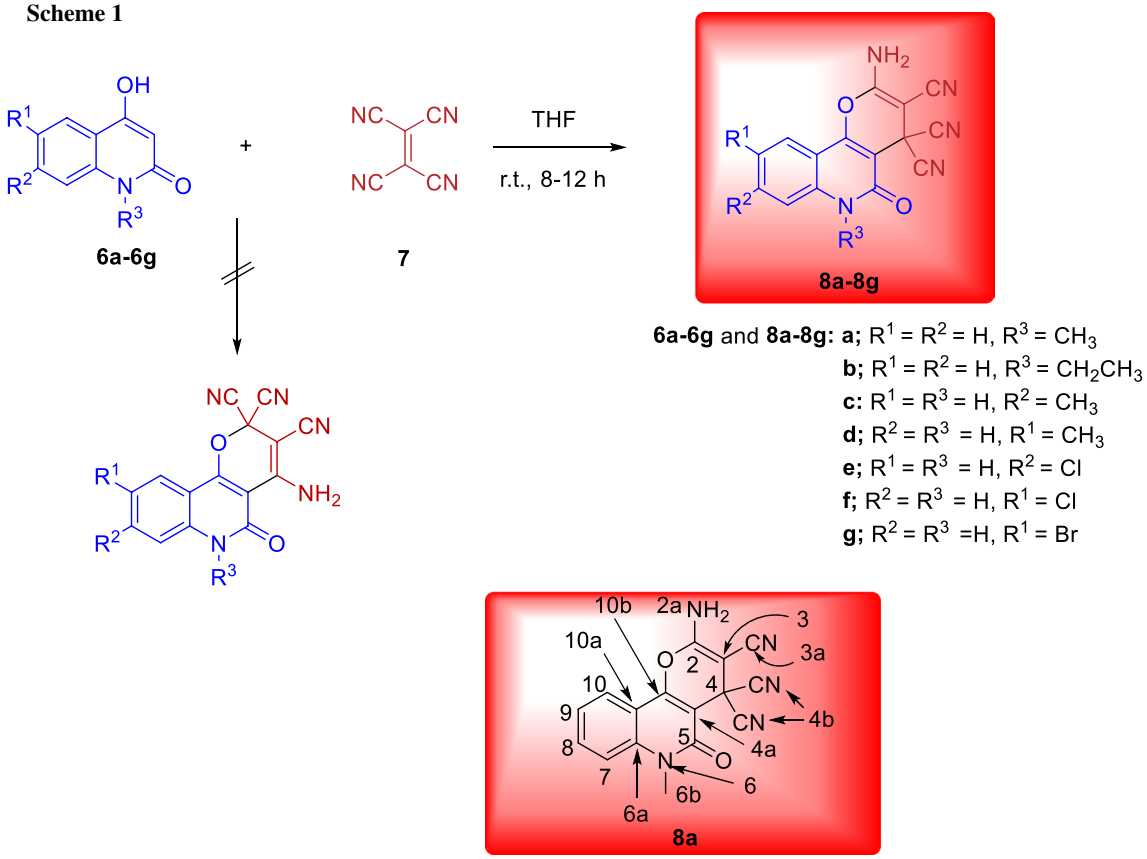
hepatic cancer (HepG2), and colorectal cancer (LS174T, HT29, and SW620) cell lines, respectively. Meanwhile, the IC_{50} values of *trans/cis*-3,4-dihydroxyhaplamine metabolites **1** and **2** were both > 200 µM [5].

Various 2,5-dialkyloxazolopyrano[3,2-*c*]quinolone derivatives **3a–3j** were evaluated for antitumor activity against three human cancer cell lines, namely MCF-7 (breast carcinoma), HepG-2 cells (human hepatocellular carcinoma), and HCT-116 (colon carcinoma) using 5-fluorouracil as a standard drug [6]. Compounds **3c** and **3f** showed higher inhibitory activity against all three tumor cell lines with having IC_{50} values in between 6.2–28.3 µg/cm^3 and 28.7–43.2 µg/cm^3, respectively (Fig. 1) [6]. Interested results were obtained among the synthesized and assigned compounds of 2'-amino-2,7-dibromo-5'-oxo-5',6'-dihydrospiro[fluorene-9,4'-pyrano[3,2-*c*]quinoline]-3'-carbonitriles **4a–4f** (Fig. 1), the derivatives of **4b**, **4c**, and **4d** showed an inhibition towards Src kinase activity with IC_{50}'s of 4.9, 5.9, and 0.9 µM, respectively [7].

Kumar et al. [8] developed fused quinolone derivatives **5a** and **5b** (Fig. 1). The obtained compounds were evaluated for their in vitro cytotoxic potential colon (HT-29, HCT-116), human lung (A549), breast (MCF-7), and prostate (PC-3 and DU145) cancer cell lines. Compound **5a** showed promising anti-proliferative activity against lung (A549) cancer cell line with an IC_{50} value of 3.17 ± 0.52 µM. Flow cytometric analyses showed that **5a**, in a dose-dependent manner, arrested both the Sub G1 and G2/M phases of the cell cycle. Also, **5b** revealed significant inhibition of tubulin polymerization and disruption of the microtubule network with an IC_{50} value of 5.15 ± 0.15 µM [8].

Previously, it was reported that pyrano[3,2-*c*]quinolin-5-one derivatives could be obtained via *a* three-component reaction of 4-hydroxyquinolin-2(1*H*)-ones with aldehydes and malononitrile. This reaction can be catalyzed by piperidine, TEBA, ammonium acetate, or triethylamine [9–12]. Also, Gunasekaran et al. showed that 6-methyl-2-(methylamino)-3-nitro-4*H*-pyrano[3,2-*c*]quinolin-5(6*H*)-ones were obtained by one-pot reaction of quinolone, (*E*)-*N*-methyl-1-(methylthio)-2-nitro-ethenamine, and aromatic aldehydes in the presence of anhydrous $ZnCl_2$ [12]. In addition, Zhu and co-workers [13] reported the synthesis of pyranoquinolinones when mixtures of quinolin-2-ones, Meldrum's acid, and aromatic aldehydes in the presence of L-proline were allowed to react in refluxing ethanol [13]. Aly et al. reported the preparation of ethyl 5,6-dihydro-2,5-dioxo-6,9-disubstituted-2*H*-pyrano[3,2-*c*]quinoline-4-carboxylates by the reaction of equimolar amounts of quinolin-2-ones

Scheme 1



and diethyl acetylenedicarboxylate in absolute ethanol containing catalytic amounts of triethylamine (Et_3N) [14]. The reaction of the *β*-keto acid derivatives with isatine was carried out under Knoevenagel reaction conditions using fused sodium acetate and glacial acetic acid. The product of this reaction was characterized as 2-(indol-3-ylidene)propanoic acid [15]. This cyclization occurred when that product was treated with concentrated sulfuric acid and formed the pyranoquinolone [15]. Furthermore, Aly et al. synthesized spiro(indoline-3,4'-pyrano[3,2-*c*]quinoline)-3'-carbonitrile by refluxing equimolar amounts of quinolin-2-ones with 2-(2-oxo-1,2-dihydroindol-3-ylidene)malononitrile in dry pyridine solution [16]. Upon refluxing quinolin-2-ones in benzene containing tributyltin(IV) chloride (Bu_3SnCl) and sodium cyanoborohydride in the presence of azobisisobutyronitrile, the reaction proceeded to give the tetracyclic pyranoquinolin-7(8*H*)-ones [17]. Bu_3SnH-mediated the radical cyclizations to the regioselective synthesis of tetracyclic heterocycles 2*H*-benzopyrano[3,2-*c*]quinolin-7(8*H*)-ones were described as general and attractive procedure due to its simplicity [17].

The multicomponent pathway describes the formation of pyrano[3,2-*c*]quinolin-5-ones has been shed light due to their decent yields coupled with easy isolation of the products and avoidance of conventional purification methods. A recent approach described that was established by the reaction of isatins with phenyl (or alkyl) sulfonyl acetonitrile and 4-hydroxy-*N*-methylquinoline-2-one [18].

As a part of our ongoing research, we aim in this paper to synthesize pyrano[3,2-*c*]quinolones **8a**–**8g** via the reaction of 4-hydroxy quinolin-2-ones **6a**–**6g** with ethene-1,2,3,4-tetracarbonitrile (TCNE, **7**).

Results and discussion

Initially, the reaction between 4-hydroxy-2-quinolin-2-ones **6a**–**6g** and ethene-1,2,3,4-tetracarbonitrile (**7**) was conducted in dry THF at room temperature. After 8–12 h, the desired pyrano[3,2-*c*]quinolones **8a**–**8g** were obtained in 75–85% yields (Scheme 1).

We carried out the reaction of **6a** with **7** under different conditions with the optimized reaction conditions in hand. On refluxing the two starting substances (entry 2, Table 1), the yield of **8a** was decreased; however, the reaction time was low. Increasing the reaction temperature might increase the oxidation of TCNE and therefore increase the side products. Similarly, adding a few drops of triethylamine or piperidine to the reaction mixture (entries 3 and 4, Table 1) did not increase the yield of **8a**, and the yields were decreased

Table 1 The reaction conditions and the yields for the formation of **8a**

Entry	Reaction condition	Yields of **8a**/%
1	THF, r.t., 8–12 h	85
2	THF, reflux 4–6 h	62
3	THF, Et_3N, r.t., 10–14 ha	74
4	THF, piperidine, r.t., 24 h[b]	76
5	EtOH, r.t., 20–24 h	62
6	EtOH, Et_3N, r.t., 20–24 ha	60
7	EtOH, piperidine, r.t., 24–30 h[b]	64
8	DMF, r.t. 24 h	80

[a]1 mmol of **6a** with 0.5 cm^3 of Et_3N

[b]1 mmol of **6a** with 0.5 cm^3 of piperidine

to 74 and 76%, respectively. Upon carrying out the reaction in polar solvents such as EtOH (entry 5, Table 1), the time taken to obtain **8a** was increased, whereas its yield was decreased.

Furthermore, adding a few drops of Et_3N or piperidine (entries 6 and 7, Table 1) did not increase the resulting yield of **8a**. Interestingly, using DMF gave a good yield of **8a**, but it was still low than THF, and the reaction took more time. In general, the best condition can be described as a high yield of pyrano[3,2-*c*]quinolones **8a**–**8g** using dry THF at room temperature (entry 1, Table 1). In addition, it was found that increasing the amount of the starting material **7** was not necessary to obtain the products **8a**–**8g** in high yield. Pyrano[3,2-*c*]quinolone derivatives **8a**–**8g** were produced by adding only equal equivalent of TCNE. High amounts of the products were obtained under standard ambient conditions, whereas the same reactions under inert atmosphere produced low yields of the products.

It appears that one of the two nucleophilic sites – C-3 and OH of the quinolone – attacks the C=C bond of TCNE, and the other attacks a nitrile group, to yield two possible products, **8a** or **8a'** (Fig. 2). To differentiate between these two suggested structures, their mass spectrometry, ^{1}H NMR, ^{1}H-^{1}H COSY, ^{13}C NMR, HMBC, ^{15} N NMR, and IR spectra were studied.

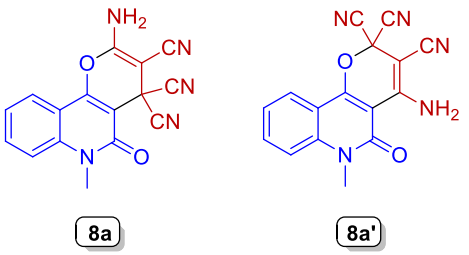


Fig. 2 Suggested structure of the product **8a** and **8a'**

The IR spectroscopy of **8a** appears several peaks characteristic for the following functional groups, two bands at $\overline{V}$ = 3296 and 3280 cm^{-1} due to NH_2 group, at 2202 cm^{-1} for the nitrile group, while at 1671 cm^{-1} for the C=O and at 1627 cm^{-1} for the Ar–C=N group. The mass spectrometry of **8a** showed a molecular ion at *m/z* = 304.1 ([M^+ + H], 60%) indicated the formation of the product via the reaction of **6a** and **7** without loss of any molecules. By studying the NMR spectrum of **8a**, the quinolone substructures can be interpreted identically, whether the structure is **8a** or **8a'**. The methyl protons H-6b are distinctive at δ_H = 3.72 ppm; their attached carbon appears at δ_C = 29.8 ppm. H-6b gives HMBC correlation with nitrogen at δ_N = 141.6 ppm, assigned as N-6, and carbons at δ_C = 158.1, 139.6, and 115.6 ppm, assigned as C-5, C-6a, and C-7 in that order; they also give weak HMBC correlation with carbon at δ_C = 96.2 ppm, assigned as C-4a; its upfield chemical shift reflects its position in a push–pull system (Table 2). N-6 also gives HMBC correlation with a 1H doublet at δ_H = 7.73 ppm, assigned as H-7; this proton gives HSQC correlation with C-7. COSY and HSQC correlations lead straightforwardly to the assignments of H-8, H-9, H-10, C-8, C-9, and C-10, as shown in Table 2. C-6a gives HMBC correlation with all four protonated aromatic carbons. H-7, H-8, and H-10 give HMBC correlation with

Table 2 NMR spectroscopic assignments of compound **8a**

^{1}H NMR	^{1}H-^{1}H COSY		Assgt
8.54 (bs, 2H)	*7.87, 7.73,* 7.49		H-2a
8.00 (d, *J* = 8.0 Hz, 1H)	*8.00,* 7.73, 7.49		H-10
	8.00, 7.87, *7.49, 3.72*		H-8
7.87 (ddd, *J* = 8.5, 7.3, 1.2 Hz, 1H)	8.00, 7.87, *7.73*		H-7
	7.73		H-9
7.73 (d, *J* = 8.6 Hz, 1H)			H-6b
7.49 (dd, *J* = 7.6, 7.6 Hz, 1H)			
3.72 (s, 3H)			
^{13}C NMR	**HSQC**	**HMBC**	**Assgt**
159.0	7.87	8.54	C-2
158.1	8.00	3.72	C-5
151.7	7.49	*8.54,* 8.00, 7.73	C-10b
139.6	7.73	8.00, 7.87, *7.73,*	C-6a
134.0	3.72	7.49, 3.72	C-8
123.1		8.00, 7.87, *7.73,*	C-10
123.0		7.49	C-9
116.4		7.87, 7.49	C-3a
115.6		7.73, 7.49	C-7
113.8		*8.00*, 3.72	C-4b
111.7		*8.00, 7.87,* 7.73	C-10a
96.2		*3.72*	C-4a
50.0		8.54	C-3
32.1		*8.54*	C-4
29.8		3.72	C-6b
^{15} N NMR	**HSQC**	**HMBC**	**Assgt**
141.6	8.54	7.73, 3.72	N-6
85.0		8.54	N-2a

carbon at $\delta_C = 111.7$ ppm, assigned as C-10a; H-10 and H-7 give HMBC correlation with carbon at $\delta_C = 151.7$ ppm, assigned as C-10b. These assignments are the same in either **8a** or **8a'**. The third ring is a pyran in either **8a** or **8a'**; it contains three carbons not shared with the quinolone substructure, three nitrile carbons (two equivalent), and an amino group. At $\delta_H = 8.54$ ppm, the amino protons give HSQC correlation with their attached nitrogen at $\delta_N = 85.0$ ppm, and HMBC correlation with all three ring carbons just mentioned as well as C-10b, which would be four bonds from the amino protons in either **8a** or **8a'**. The two equivalent nitrile carbons appear upfield of the unique nitrile, at $\delta_C = 116.4$ vs. 113.8 ppm; the latter is α,β-unsaturated. These assignments, too, do not differentiate the structures. The calculated ^{13}C shifts for **8a** are considerably closer to observation than those for **8a'** (rms deviation 11.6 vs. 20.0 for the five carbons with different shifts). In particular, the carbon bearing two nitriles is farther upfield in **8a**, in which it is attached only to carbons as C-4, than in **8a'**, in which it is attached to oxygen as C-2. The other large change is in C-3, which is in a push–pull system in either structure, but receives electron donation from both O and N in **8a** (Table 2).

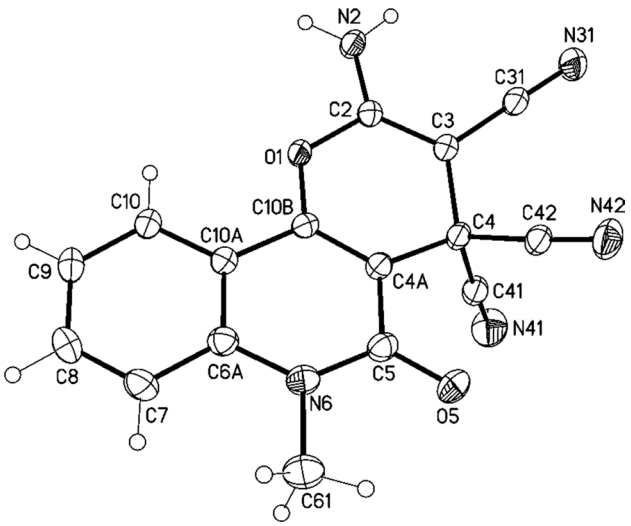


Fig. 3 X-ray structure analysis of compound **8a** (displacement parameters are drawn at 30% probability level)

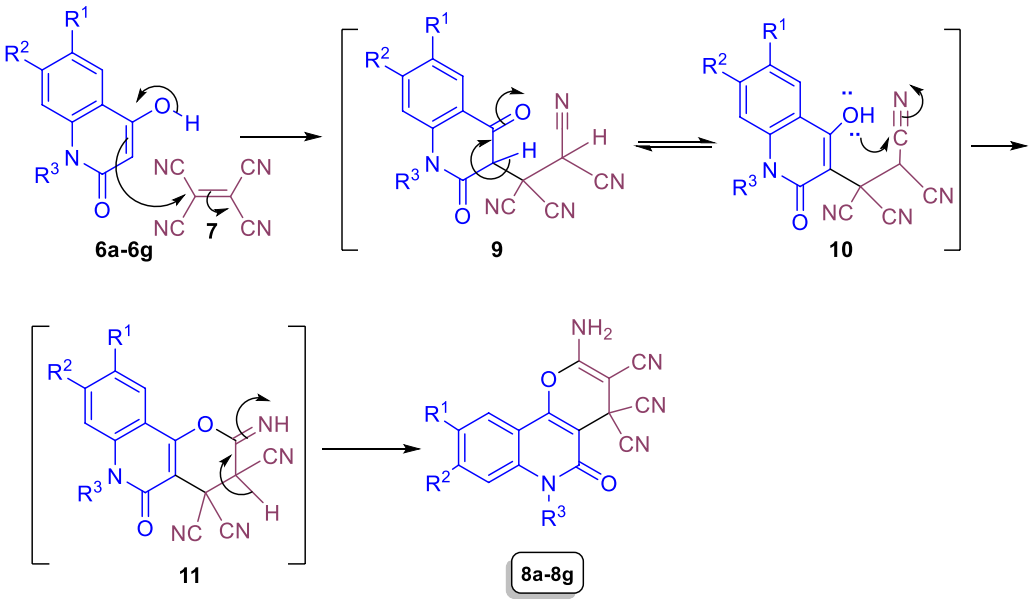
Single-crystal X-ray analysis provided strong support for the structure of **8a** (Fig. 3). The same structure was suggested for the other derivatives **8b**-**8 g** based on their similarities in NMR spectroscopic analysis.

The mechanism describing the product's formation was based upon nucleophilic addition of C-3 in compounds **6a**–**6g** to the electrophilic carbon of **7**, which would give intermediate **9** (Scheme 2). The intermediate **9** would then exist in tautomerism with intermediate **10**. After that, cyclization was occurred by the nucleophilic attack of the OH lone pair to the carbonitrile-carbon to give the intermediate **11**. Finally, hydrogen shift accompanied with aromatization would give compounds **8a**–**8g** (Scheme 2).

Conclusion

This work focused on synthesizing new heteroannulated pyrano[3,2-*c*]quinolones. By applying reaction between 4-hydroxyquinolin-2-one derivatives **6a**–**6g** and ethene-1,2,3,4-tetracarbonitrile (TCNE, **7**), pyrano[3,2-*c*]quinolones **8a**–**8g** were obtained in good yield (75–85%). Non-polar

Scheme 2



and neutral conditions were considered the best ones to obtain high yields of the target products. Therefore, prospective work in our lab involving the reactions of quinolone derivatives with bi-electrophilic compounds under similar conditions would be interesting.

Experimental

Melting points were taken in open capillaries on a Gallenkamp melting point apparatus (Weiss–Gallenkamp, Loughborough, UK). The IR spectra were recorded from potassium bromide disks with an FT device (Germany). Elemental analyses were carried out at the Perkin-Elmer Elemental analyzer (Germany). The NMR spectra were measured in DMSO-d_6 on a Bruker AV-400 spectrometer (400 MHz for ^{1}H, 100 MHz for ^{13}C, and 40.55 MHz for ^{15} N); and the chemical shifts are expressed in δ (ppm), versus internal tetramethylsilane (TMS) = 0 ppm for ^{1}H and ^{13}C, and external liquid ammonia = 0 ppm for ^{15} N. Coupling constants are stated in Hz. Using ^{1}H-^{1}H COSY, ^{1}H-^{13}C, and ^{1}H-^{15} N HSQC and HMBC experiments, correlations were established. Mass spectra were recorded on a Finnigan Fab 70 eV (Germany), Institute of Organic Chemistry, Karlsruhe University, Karlsruhe, Germany. TLC was performed on analytical Merck 9385 silica aluminum sheets (Kieselgel 60) with Pf_{254} indicator; TLC's were viewed at λ_{max} = 254 nm. Elemental analyses for C, H, N were carried out with Elementar 306.

1,6-Disubstituted-quinoline-2,4-(1*H*,3*H*)-diones **6a–6g** were prepared according to the literature [19]. TCNE (**7**) was bought from Aldrich.

The reaction of 6a–6g with TCNE (7): synthesis of compounds 8a–8g A suspension of 1,6-disubstituted quinoline-2,4-(1*H*,3*H*)-diones **6a–6g** (1 mmol) in 20 cm^3 dry tetrahydrofuran (THF) was added to a solution of 0.128 g TCNE (**7**, 1 mmol) in 15 cm^3 dry THF. The reaction mixture was stirred for 20–25 h until the reactants disappeared (monitored by TLC). The resulting precipitates of **8a–8g**, obtained on cold, was filtered off and dried. The precipitates were recrystallized from the stated solvents.

2-Amino-5,6-dihydro-6-methyl-5-oxo-4*H*-pyrano[3,2-*c*]-quinoline-3,4,4-tricarbonitrile (8a, $C_{16}H_9N_5O_2$) Yellow crystals (DMF); yield: 0.280 g (85%); m.p.: 336–338 °C; IR (KBr): $\overline{V}$ = 3296, 3280 (NH_2), 2202 (CN), 1671 (CO), 1627 (Ar–C = N) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.54 (bs, 2H, H-2a), 8.00 (d, J = 8.0 Hz, 1H, H-10), 7.87 (ddd, J = 8.5, 7.3, 1.2 Hz, 1H, H-8), 7.73 (d, J = 8.6 Hz, 1H, H-7), 7.49 (dd, J = 7.6, 7.6 Hz, 1H, H-9), 3.72 (s, 3H, H-6b) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 159.0 (C-2), 158.1 (C-5), 151.7 (C-10a), 139.6 (C-6a), 134.0 (C-8), 123.1 (C-10), 123.0 (C-9), 116.4 (C-3a), 115.6 (C-7), 113.8 (C-4b), 111.7 (C-10a), 96.2 (C-4a), 50.0 (C-3), 32.1 (C-4), 29.8 (C-6b) ppm; ^{15} N NMR (40.55 MHz, DMSO-d_6): δ = 141.6 (N-6), 85.0 (N-2a) ppm; MS (FAB, 70 eV): *m/z* (%) = 304.1 ([M + H]$^+$, 65).

4-Amino-5,6-dihydro-6-ethyl-5-oxo-4*H*-pyrano[3,2-*c*]quinoline-3,4,4-tricarbonitrile (8b, $C_{17}H_{11}N_5O_2$) Brown crystals (DMF/EtOH); yield: 0.252 g (80%); m.p.: 342–344 °C; IR (KBr): $\overline{V}$ = 3346, 3334 (NH_2), 2201 (CN), 1644 (CO), 1622 (Ar–C = N) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.53 (s, 2H, H-2a), 8.02 (dd, J = 8.1, 1.1 Hz, 1H, H-10), 7.87 (ddd, J = 8.5, 7.2, 1.4 Hz, 1H, H-8), 7.79 (d, J = 8.6 Hz, 1H, H-7), 7.48 (dd, J = 7.7, 7.3 Hz, 1H, H-9), 4.38 (q, J = 7.0 Hz, 2H, H-6b), 1.27 (t, J = 7.0 Hz, 3H, H-6c) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 159.1 (C-2), 157.8 (C-5), 151.8 (C-10b), 138.5 (C-6a), 134.1 (C-8), 123.4 (C-10), 122.9 (C-9), 116.4 (C-3a), 115.3 (C-7), 113.8 (2C-4b), 111.9 (C-10a), 96.1 (C-4a), 49.9 (C-3), 37.5 (C-6b), 32.0 (C-4), 12.7 (C-6b) ppm; ^{15} N NMR (40.55 MHz, DMSO-d_6): δ = 155.0 (N-6), 85.3 (N-2a) ppm; MS (FAB, 70 eV): *m/z* (%) = 318.1 ([M + H]$^+$, 60).

4-Amino-5,6-dihydro-8-methyl-5-oxo-4*H*-pyrano[3,2-*c*]-quinoline-3,4,4-tricarbonitrile (8c, $C_{16}H_9N_5O_2$) Brown crystals (DMF/EtOH); yield: 0.273 g (83%); m.p.: 320–322 °C; IR (KBr): $\overline{V}$ = 3333, 3320 (NH_2), 3174 (NH), 2209 (CN), 1671 (CO), 1646 (Ar–C=N) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.45 (b, 1H, NH-6), 8.53 (b, 2H, H-2a), 7.73 (bs, 1H, H-10), 7.50 (bd, J = 8.5 Hz, 1H, H-9), 7.25 (d, J = 8.4 Hz, 1H, H-7), 2.45 (s, 3H, H-8a) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 159.2 (C-2), 158.3 (C-5), 152.6 (C-10b), 136.9 (C-6a), 134.7 (C-9), 132.2 (C-8), 121.7 (C-10), 116.5 (C-3a), 115.8 (C-7), 113.9 (2C-4b), 111.9 (C-10a), 96.5 (C-4a), 49.1 (C-3), 31.3 (C-4), 20.5 (C-8a) ppm; MS (FAB, 70 eV): *m/z* (%) = 304.2 ([M + H]$^+$, 45).

4-Amino-5,6-dihydro-9-methyl-5-oxo-4*H*-pyrano[3,2-*c*]quinoline-3,4,4-tricarbonitrile (8d, $C_{16}H_9N_5O_2$) Brown crystals (DMF); yield: 0.260 g (79%); m.p.: 308–310 °C; IR (KBr): $\overline{V}$ = 3334, 3322 (NH_2), 3174 (NH), 2219 (CN), 1672 (CO), 1649 (Ar–C = N) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.43 (b, 1H, NH-6), 8.49 (b, 2H, H-2a), 7.70 (bs, 1H, H-10), 7.58 (bd, J = 8.5 Hz, 1H, H-8), 7.36 (d, J = 8.4 Hz, 1H, H-7), 2.40 (s, 3H, H-9a) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 159.1 (C-2), 158.5 (C-5), 152.5 (C-10b), 136.9 (C-6a), 134.9 (C-8), 132.1 (C-9), 121.9 (C-10), 116.4 (C-3a), 115.9 (C-7), 113.8 (2C-4b), 110.8 (C-10a), 96.4 (C-4a), 49.9 (C-3), 31.5 (C-4), 20.6 (C-9a) ppm; ^{15} N NMR (40.55 MHz, DMSO-d_6): δ = 146.8 (N-6), 85.5 (N-2a) ppm; MS (FAB, 70 eV): *m/z* (%) = 304.2 ([M + H]$^+$, 35).

2-Amino-8-chloro-5,6-dihydro-5-oxo-4*H*-pyrano[3,2-*c*]quinoline-3,4,4-tricarbonitrile (8e, $C_{15}H_6ClN_5O_2$) Brown crystals (DMF/H_2O); yield: 0.232 g (75%); m.p.: 336–338 °C; IR (KBr): $\overline{V}$ = 3333, 3324 (NH_2), 3193 (NH), 2213 (CN), 1691 (CO), 1650 (Ar–C = N) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 12.50 (b, 1H, NH-6), 8.88 (b, 2H, H-2a), 7.35 (bs, 1H, H-10), 7.10 (bd, J = 8.5 Hz, 1H, H-9), 7.70 (d, J = 8.4 Hz, 1H, H-7) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 159.1 (C-2), 158.2 (C-5), 152.5 (C-10b), 136.9 (C-6a), 134.2 (C-8), 129.7 (C-10), 125.8 (C-9), 119.8 (C-7), 116.5 (C-3a), 113.9 (2C-4b), 111.8 (C-10a), 96.5 (C-4a), 50.1 (C-3), 31.3 (C-4) ppm; MS (FAB, 70 eV): *m/z* (%) = 324.1 ($[M+H]^+$, 45).

2-Amino-9-chloro-5,6-dihydro-5-oxo-4*H*-pyrano[3,2-*c*]quinoline-3,4,4-tricarbonitrile (8f, $C_{15}H_6ClN_5O_2$) Brown crystals (DMF/MeOH); yield: 0.247 g (80%); m.p.: 342–344 °C; IR (KBr): $\overline{V}$ = 3360, 3345 (NH_2), 3279 (NH), 2215 (CN), 1674 (CO), 1605 (Ar–C = N) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 11.88 (s, 1H, NH-6), 8.55 (b, 2H, H-2a), 7.72–7.61 (m, 1H, H-10), 7.60–7.53 (m, 1H, H-8), 7.45–7.31 (m, 1H, H-7) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 168.3 (C-2), 164.8 (C-5), 164.2 (C-10b), 162.9 (C-6a), 139.6 (C-9), 137.9 (C-10), 133.1 (C-8), 122.9 (C-7), 116.3 (C-3a), 113.3 (2C-4b), 100.5 (C-10a), 98.1 (C-4a), 51.3 (C-3), 35.7 (C-4) ppm; MS (FAB, 70 eV): *m/z* (%) = 324.1 ($[M+H]^+$, 40).

2-Amino-9-bromo-5,6-dihydro-5-oxo-4*H*-pyrano[3,2-*c*]quinoline-3,4,4-tricarbonitrile (8 g, $C_{15}H_6BrN_5O_2$) Brown crystals (DMF/MeOH); yield: 0.215 g (78%); m.p.: 304–306 °C; IR (KBr): $\overline{V}$ = 3376, 3350 (NH_2), 3179 (NH), 2297 (CN), 1678 (CO), 1638 (Ar–C = N) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 12.62 (s, 1H, NH-6), 8.51 (b, 2H, H-2a), 8.07 (d, J = 2.3 Hz, 1H, H-10), 7.91 (dd, J = 8.9, 2.3 Hz, 1H, H-8), 7.40 (d, J = 8.9 Hz, 1H, H-7) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 159.5 (C-2), 159.0 (C-5), 152.4 (C-10b), 138.3 (C-6a), 136.6 (C-9), 125.4 (C-10), 118.8 (C-8), 116.8 (C-7), 115.1 (C-3a), 114.1 (2C-4b), 113.3 (C-10a), 98.2 (C-4a), 50.3 (C-3), 34.7 (C-4) ppm; MS (FAB, 70 eV): *m/z* (%) = 368.1 ($[M]^+$, 45).

Crystal structure determination of 8a

The single-crystal X-ray diffraction study was carried out on a Bruker D8 Venture diffractometer with PhotonII detector at 298(2) K using Cu-Ka radiation (λ = 1.54178 Å). Dual space methods (SHELXT) [20] were used for structure solution, and refinement was carried out using SHELXL-2014 (full-matrix least-squares on F^2) [21]. Hydrogen atoms were localized by difference electron density determination and refined using a riding model (H(N) free). Semi-empirical absorption corrections and extinction corrections were applied.

8a: yellow crystals, $C_{16}H_9N_3O_2$, M_r = 303.28, crystal size 0.18 × 0.14 × 0.04 mm, monoclinic, space group $P2_1/c$ (No. 14), a = 5.9873(1) Å, b = 14.9471(2) Å, c = 15.3227(2) Å, β = 91.016(1)°, V = 1371.06(3) $Å^3$, Z = 4, ρ = 1.469 Mg m^{-3}, μ(Cu-K_α) = 0.85 mm^{-1}, $F(000)$ = 624, T = 298 K, $2\theta_{max}$ = 144.2°, 16,614 reflections, of which 2708 were independent (R_{int} = 0.057), 216 parameters, 2 restraints, R_1 = 0.042 (for 2491 $I > 2\sigma(I)$), wR_2 = 0.118 (all data), S = 1.03, largest diff. peak / hole = 0.22 / -0.19 e $Å^{-3}$.

CCDC 2,115,414 (**8a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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