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ORIGINAL PAPER

Formation of furo[3,2-*c*]quinolone-2-carbonitriles and 4-oxo-4,5-dihydrofuro[3,2-*c*]quinolone-2-carboxamides from reaction of quinoline-2,4-diones with 2-[bis(methylthio)-methylene]malononitrile

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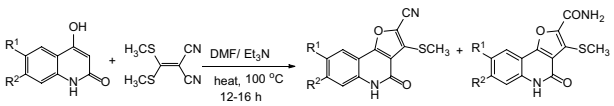
Abstract

Quinoline-2,4-diones reacted with 2-[bis(methylthio)methylene]malononitrile in DMF/Et_3N to produce 3-(methylthio)-4-oxo-4,5-dihydrofuro[3,2-*c*]quinolone-2-carbonitriles and 3-(methylthio)-4-oxo-4,5-dihydrofuro[3,2-*c*]quinolone-2-carboxamides in state of 2-imino-substituted 4-(methylthio)-5,6-dihydro-2*H*-pyrano[3,2-*c*]quinolone-3-carbonitriles. The structures of all new products were proved using NMR, IR, and mass spectral data. The possible mechanism for the reaction is also discussed.

Graphic abstract



Keywords Quinolin-2,4-diones · 2-[Bis(methylthio)methylene]malononitrile · Furo[3,2-*c*]quinolone-3-carbonitriles · Mechanism

Introduction

2-Quinolones possess very promising biological activities such as anticonvulsant [1–3], antibacterial [4], anti-Alzheimer [5], antimicrobial [6], anti-dermatities [7], anti-cancer [8], and pain relief [9], in addition to their medical, agricultural, and industrial uses [10–12]. As an example, camptothecin (**I**, Fig. 1) is an anticancer agent and a secondary metabolite damaging the DNA and consequently annihilation of the targeted cell. Topotecan hydrochloride (**II**) is also one of such compounds that acts as topoisomerase inhibitor and is best used for various kinds of cancer treatments, especially lung cancer and ovarian cancer [13, 14].

To extend the knowledge around the new fused quinolones compounds, we focused our searches on synthesizing a new class of compounds which we expect will have important activities in medicinal and industrial area. Previously, Aly et al. synthesized 2,3-bis(4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)succinic acid derivatives from the reaction of one equivalent of aromatic amines with two equivalents of diethyl malonate in diphenyl ether and catalyzed with triethylamine [15]. On reacting four equivalents of 4-hydroxyquinolin-2(1*H*)-ones with one equivalent of acenaphthoquinone in absolute ethanol, containing catalytic Et_3N, the reaction gave acenaphthylene-1,1,2,2-tetrayltetrakis(4-hydroxyquinolin-2(1*H*)-ones)

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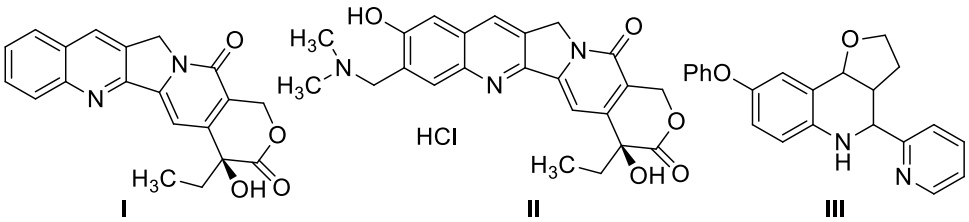


Fig. 1 Anticancer and antifungal activities of quinolones **I**–**III**

[16]. We also reported that quinoline-2,4-diones reacted with 2-(2-oxo-1,2-dihydroindol-3-ylidene)malononitrile in pyridine to produce spiro[indoline-3,4′-pyrano[3,2-*c*]-quinolone]-3′-carbonitriles [17]. The same target materials of 2-quinolones reacted with diethyl acetylenedicarboxylate in absolute ethanol to give pyrano[3,2-*c*]quinoline-4-carboxylates [18]. We have also recently reported that a class of 1,2,3-triazoles derived by 2-quinolone [19] has been synthesized, via Cu-catalyzed [3 + 2]-cycloadditions (Meldal-Sharpless 'click'-reactions) of 4-azidoquinolin-2(1*H*)-ones with ethyl propiolate [19]. We also obtained fused naphthofuro[3,2-*c*]quinoline-6,7,12-triones and pyrano[3,2-*c*]quinoline-6,7,8,13-tetraones that have shown potential as ERK inhibitors [20]. While synthesized bis(6-substituted-4-hydroxy-2-oxo-1,2-dihydro-quinolin-3-yl)-naphthalene-1,4-diones and substituted *N*-(alkyl)bis-quinolinone triethyl-ammonium salts were explored as candidates for extracellular signal-regulated kinases 1/2 (ERK1/2) having antineoplastic activity [21].

Synthesis of furo[3,2-*c*]quinolones has shed interest on organic synthesis [22, 23]. Furoquinolones are important structural motifs in the domain of medicinal chemistry due to their myriad biological activities. These class of compounds have been shown to possess potential activities like antimalarial [24], antibacterial [25], anticancer [26], antiemetic [27]. Furo[3,2-*c*]quinolone **III** (Fig. 1) was previously synthesized and its preliminary anticancer activity and antifungal potential were investigated. This compound showed potential anticancer activity against MDAMB-231 breast cancer cells. Meanwhile, it could enhance the fungistatic activity of miconazole against *Candida albicans* [28]. Moreover, furo[3,2-*c*]quinolones showed activity as a lipoxygenase inhibitor [29]. For all these reasons, synthesis of furo[3,2-*c*]quinolines continues to attract interest. Herein, we describe the synthesis of a class of new furo[3,2-*c*]quinolones, via the reaction of quinoline-2,4-(1*H*,3*H*)-diones **1a**–**1f** with 2-[bis(methylthio)methylene]malononitrile (**2**).

Results and discussion

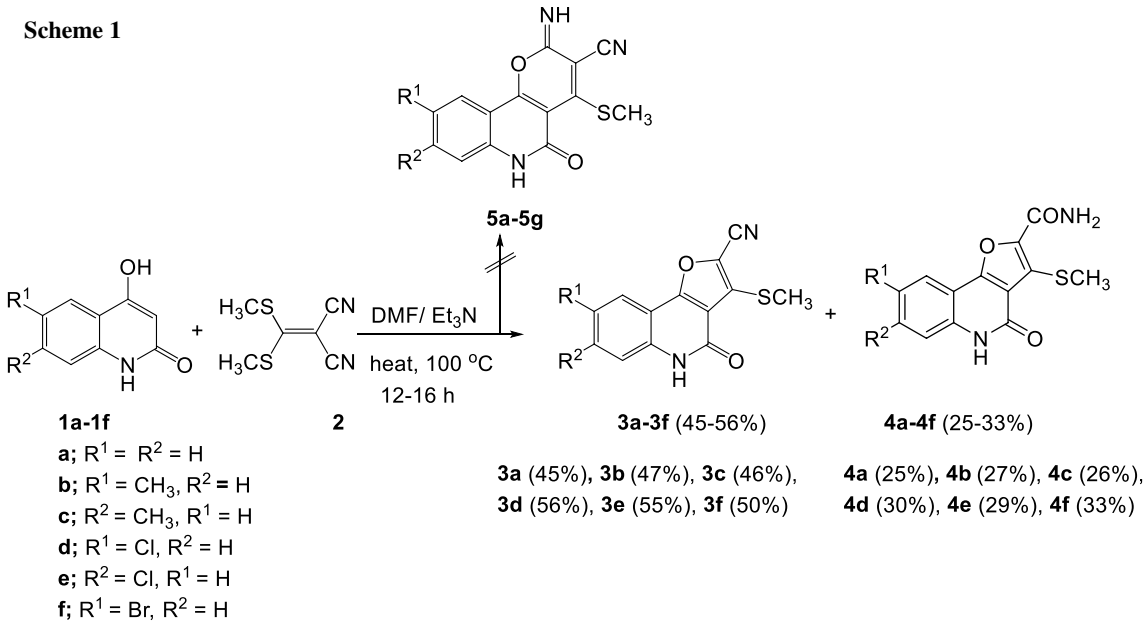
Heating at 100 °C of equimolar amounts of 6,7-disubstituted quinoline-2,4-(1*H*,3*H*)-diones **1a**–**1f** with 2-[bis(methylthio)methylene]malononitrile (**2**) in dry DMF and catalyzed by Et_3N led to the formation of 3-(methylthio)-4-oxo-4,5-dihydrofuro[3,2-c]quinolone-2-carbonitriles **3a**–**3f** and 3-(methylthio)-4-oxo-4,5-dihydrofuro[3,2-c]quinolone-2-carboxamides **4a**–**4f** in 45–56% and 25–33% yields, respectively (Scheme 1).

To confirm the structures of all the obtained products, elemental analyses, IR, NMR and mass spectra were performed; these and elemental analyses were in good agreement with the assigned structures. To illustrate the structure elucidation, we choose a representative example, 3-(methylthio)-4-oxo-4,5-dihydrofuro[3,2-*c*]quinolone-2-carbonitrile (**3a**). According to elemental analysis and mass spectrometry, compound **3a** has a molecular formula of $C_{13}H_8N_2O_2S$, resulting from combination of one molecule of quinoline-2,4-dione (**1a**) with one molecule of **2** accompanied with extrusion of a molecule of HCN. The structure of **3a** (Fig. 2) was supported by its ^{1}H NMR spectrum, which revealed a double-doublet at $\delta_H = 8.00$ ppm and a multiplet at 7.50–7.20 ppm related to the remaining three aromatic protons. The NH and SCH_3 protons appear as two singlets at 12.20 ppm and 2.00 ppm. The ^{13}C NMR spectrum showed the SCH_3, CO, and C-9b and carbonitrile carbons at $\delta_C = 13.1$ ppm, 164.0 ppm, 158.0 ppm, and 110.8 ppm, respectively (see the experimental section).

Another example as in **3b** (Fig. 2), elemental analysis and mass spectrometry has the gross formula $C_{14}H_{10}N_2O_2S$. The ^{1}H NMR spectrum showed three singlets at $\delta_H = 12.00$ ppm for NH-quinlone, 2.10 ppm for CH_3, and 2.15 ppm for SCH_3 protons. The aromatic protons system appears between 7.20 and 6.98 ppm. The H-9 appears as a broad singlet at 8.07 ppm, whereas its carbon resonated at $\delta_C = 132.00$ ppm. The ^{13}C spectrum has 14 lines, consistent with **3b**; eleven are in the normal sp^2 region between 123.8 and 164.4 ppm. Two carbons at 111.0 ppm and 158.2 ppm were related to carbonitrile and C-9b. The SCH_3 and the carbonyl carbons resonated at = 13.8 ppm and 164.4 ppm.

In case of compounds **4a**–**4f**, the IR spectrum of **4a**, as an example, showed NH and NH_2 stretching at $\overline{\nu} = 3100$–3300 cm^{-1}, whereas the carbonyl groups absorbed at 1660 and 1640 cm^{-1}. Through elemental analysis and mass spectrometry, it is seen that compound **4a** (Fig. 3) has a molecular formula of $C_{13}H_{10}N_2O_3S$, resulting from combination of one molecule of quinoline-2,4-dione (**1a**) with one molecule of **2** accompanied with extrusion of a molecule of HCN and addition of one molecule of water. The ^{1}H NMR spectroscopic data of **4a** (Fig. 3) revealed a double-doublet

Scheme 1



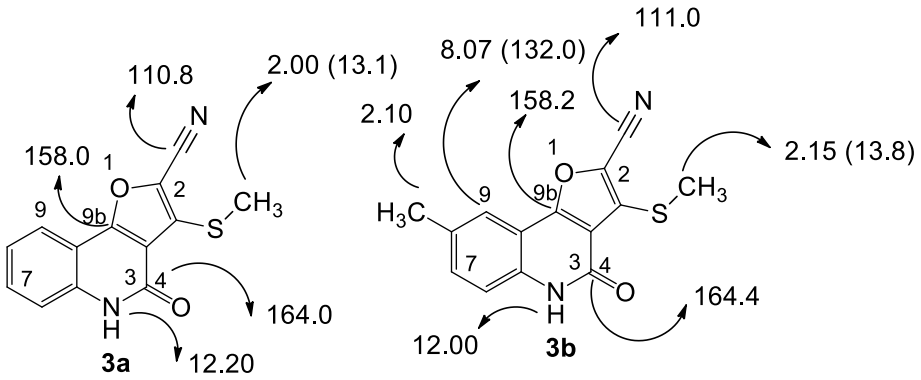


Fig. 2 Distinctive carbons and protons of compounds **3a**, **3b** and their δ_{ppm} values

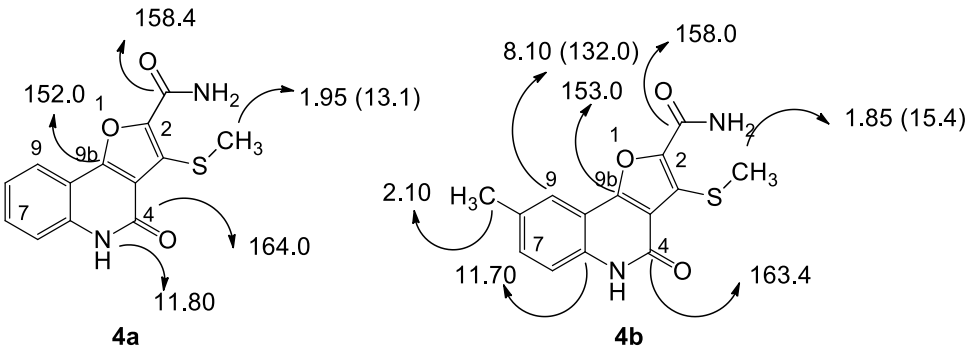


Fig. 3 Distinctive carbons and protons of compounds **4a**, **4b** and their δ_{ppm} values

at $\delta_H = 8.00$ ppm and a multiplet at 7.10–6.90 ppm related to the four aromatic and NH_2 protons, whereas the NH_2 protons superimposed the aromatic protons. The NH and SCH_3 protons appear as two singlets at 11.80 ppm and 1.95 ppm. The ^{13}C NMR spectrum showed the carbonyl-quinolone, carboxamide, SCH_3, and C-9b carbons at $\delta_C = 164.0$ ppm, 158.4 ppm, 13.1 ppm, and 152.0 ppm, respectively (see the experimental section). In case of **4b**, its ^1H NMR spectrum showed H-9 as a broad singlet at $\delta_H = 8.10$ ppm, whereas the NH, CH_3-8, and SCH_3 protons resonated as three singlets at 11.70 ppm, 2.10 ppm, and 1.85 ppm, respectively. The ^{13}C NMR spectrum revealed CH-9, C-9b, carbonyl amide-, and carbonyl-quinolone-carbons at $\delta_C = 132.0$ ppm, 153.0 ppm, 158.0 ppm, and 163.4 ppm, respectively.

We propose the mechanism shown in Scheme 2. Salt formation of intermediate **A** is formed due to abstraction of a proton from **1** by Et_3N. Conjugate addition of **A** to **2**, catalyzed by base, would give intermediate **B**. Elimination of methylthiol from **B** would give intermediate **C**. Two proposed routes would be: route (1) a nucleophilic attack of the oxygen lone pair to electrophilic carbon assigned as $=C(CN)_2$ accompanied with elimination of HCN molecule would directly proceed to give **3**, or route (2) favorable addition of the oxygen lone pair to the nitrile carbon would give Zwitter ion **D**, which on neutralization would give the expected pyranoquinolone **5**. Thereafter, ring cleavage and rearrangement of **5** accompanied by elimination of HCN molecule would give **3**. Partial hydrolysis of **3** under reaction condition would give **4**.

Conclusion

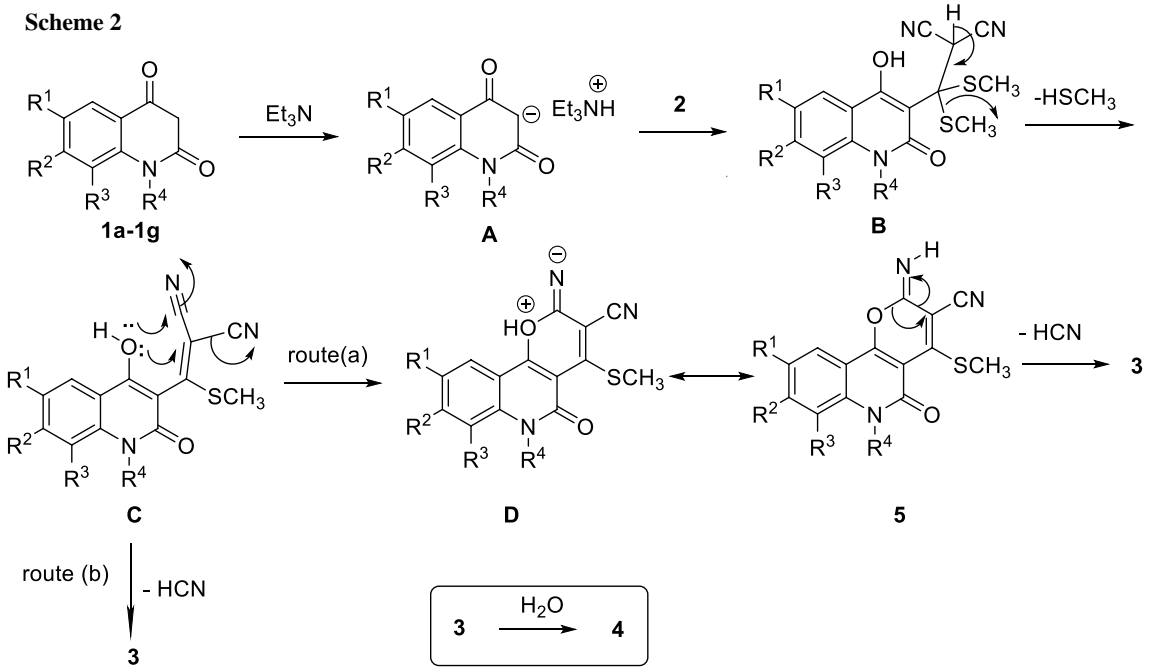
Reaction of 2,4-quinolones with 2-[bis(methylthio)methylene]malononitrile in DMF/Et_3N gave two products; one as major product assigned as 3-(methylthio)-4-oxo-4,5-dihydrofuro[3,2-*c*]quinolone-2-carbonitriles and 3-(methylthio)-4-oxo-4,5-dihydrofuro[3,2-*c*]quinolone-2-carboxamides as minor product.

Experimental

NMR spectra were measured in DMSO-d_6 on a Bruker AV-400 spectrometer (Bruker BioSpin Corp., Billerica, MA, USA) (400.13 MHz for ^{1}H, 100.13 MHz for ^{13}C) at Florida Institute of Technology, USA. The ^{1}H and ^{13}C chemical shifts are given relative to internal standard TMS. For preparative thin layer chromatography (PLC), glass plates (20 × 48 cm) were covered with a slurry of silica gel Merck PF254 and air dried and developed using the solvents listed. Zones were detected by quenching of indicator fluorescence upon exposure to 254 nm UV light. Elemental analyses were carried in the National Research Center, Dokki, and Cairo, Egypt. Mass spectrometry was performed by electron impact at 70 eV, with a Finnigan Mat 8430 spectrometer in the National Research center, Dokki, Cairo, Egypt. IR spectra using KBr pellets were run on a FT-IR (Bruker), Minia University, El-Minia, Egypt. Starting materials quinoline-2,4-diones **1a–1f** were prepared according to the literature [30].

General procedure for synthesis of 3a–3f and 4a–4f

A 100 cm^3 round-bottom flask was flame-dried, a mixture of **1a–1f** (1 mmol), **2** (1 mmol), 50 cm^3 DMF, and 0.5 cm^3 of Et_3N was refluxed for 12–16 h with stirring (the reaction was followed by TLC analysis). After the reaction's completion, the formed products **3a–3f** were filtered off. The filtrate was



then concentrated to half its volume. The second products **4a**–**4f** were obtained by filtration. All products **3a**–**3f** and **4a**–**4f** were recrystallized from the stated solvents.

3-(Methylthio)-4-oxo-4,5-dihydrofuro[3,2-*c*]quinoline-2-carbonitrile (3a, $C_{13}H_8N_2O_2S$) Yield: 0.115 g (45%); colorless crystals (DMF/EtOH); m.p.: 298–300 °C; R_f = 0.5 (toluene: AcOEt 5:1); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.20 (bs, 1H, NH), 7.90 (dd, J = 7.7, 1.5 Hz, 1H, H-9), 7.50–7.20 (m, 3H, Ar–H), 2.00 (s, 3H, SCH_3) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 164.0 (C-4), 158.0 (C-9b), 132.5, 132.0, 131.4, 129.8 (Ar–C), 128.0, 126.4, 125.5 (Ar–CH), 124.2, 123.0 (Ar–C), 110.8 (CN), 13.1 (SCH_3) ppm; MS (FAB, 70 eV): *m/z* (%) = 256 (M^+, 60); IR (KBr): $\overline{\nu}$ = 3230 (NH), 3099 (Ar–H), 2205 (CN), 1640 (C = O), 1600 (Ar–C = N), 1596 (Ar–C = C) cm^{-1}.

8-Methyl-3-(methylthio)-4-oxo-4,5-dihydrofuro[3,2-*c*]quinoline-2-carbonitrile (3b, $C_{14}H_{10}N_2O_2S$) Yield: 0.127 g (47%); colorless crystals (DMF); m.p.: 310–312 °C; R_f = 0.45 (toluene: AcOEt 5:1); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.00 (bs, 1H, NH), 8.07 (bs, 1H, H-9), 7.20–6.98 (m, 2H, Ar–H), 2.10 (s, 3H, CH_3), 2.15 (s, 3H, SCH_3) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 164.4 (C-4), 158.2 (C-9b), 139.0 (Ar–C-CH_3), 134.0 (Ar–C), 132.0 (Ar–CH-9), 131.0, 128.6 (Ar–C), 128.2, 125.4 (Ar–CH), 124.6, 123.8 (Ar–C). 111.0 (CN), 22.0 (CH_3), 13.8 (SCH_3) ppm; IR (KBr): $\overline{\nu}$ = 3240 (NH), 3070 (Ar–H), 2210 (CN), 1645 (C = O), 1610, 1596 (Ar–C = N, Ar–C = C) cm^{-1}; MS (FAB, 70 eV): *m/z* (%) = 270 (M^+, 40).

7-Methyl-3-(methylthio)-4-oxo-4,5-dihydrofuro[3,2-*c*]quinoline-2-carbonitrile (3c, $C_{14}H_{10}N_2O_2S$) Yield: 0.124 g (46%); colorless crystals (DMF/H_2O); m.p.: 315–317 °C; R_f = 0.55 (toluene: AcOEt 5:1); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.90 (bs, 1H, NH), 8.12 (bs, 1H, H-9), 7.40–7.20 (m, 2H, Ar–H), 2.25 (s, 3H, CH_3), 2.00 (s, 3H, SCH_3) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 164.8 (C-4), 158.0 (C-9b), 134.5 (Ar–C-CH_3), 134.2 (Ar–C), 132.2 (Ar–CH-9), 131.0, 128.6 (Ar–C), 128.2, 125.4 (Ar–CH), 124.6, 123.8 (Ar–C), 110.8 (CN), 22.2 (CH_3), 13.5 (SCH_3) ppm; IR (KBr): $\overline{\nu}$ = 3230 (NH), 3065 (Ar–H), 2212 (CN), 1648 (C = O), 1615 (Ar–C = N), 1590 (Ar–C = C) cm^{-1}; MS (FAB, 70 eV): *m/z* (%) = 270 (M^+, 40).

8-Chloro-3-(methylthio)-4-oxo-4,5-dihydrofuro[3,2-*c*]quinoline-2-carbonitrile (3d, $C_{13}H_7ClN_2O_2S$) Yield: 0.162 g (56%); colorless crystals (DMF); m.p.: 292–294 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.88 (bs, 1H, NH), 7.80 (d, J = 0.7 Hz, 1H, H-9), 7.20–6.90 (m, 2H, Ar–H), 1.95 (s, 3H, SCH_3) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 163.9 (C-4), 158.0 (C-9b), 136.4, 134.0, 133.0 (Ar–C), 132.2 (Ar–CH-9), 128.4 (Ar–C-Cl), 127.4, 126.2 (Ar–CH), 124.0, 123.4 (Ar–C). 111.2 (CN), 13.8 (SCH_3) ppm; IR (KBr): $\overline{\nu}$ = 3225 (NH), 3070 (Ar–H), 2212 (CN), 1645 (C = O), 1618 (Ar–C = N), 1590 (Ar–C = C) cm^{-1}; MS (FAB, 70 eV): *m/z* (%) = 292 ($[M+2]^+$, 34), 290 (M^+, 50).

7-Chloro-3-(methylthio)-4-oxo-4,5-dihydrofuro[3,2-*c*]quinoline-2-carbonitrile (3e, $C_{13}H_7ClN_2O_2S$) Yield: 0.160 g (55%); colorless crystals (DMF); m.p.: 322–324 °C; R_f = 0.4 (toluene: AcOEt 5:1); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.90 (bs, 1H, NH), 6.90–6.70 (m, 3H, Ar–H)), 1.95 (s, 3H, SCH_3) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 163.2 (C-4), 157.8 (C-9b), 136.0 (Ar–C), 134.4 (Ar–CH-9), 133.0, 131.0 (Ar–C), 128.0 (Ar–C-Cl), 127.1, 126.0 (Ar–CH), 122.2, 120.0 (Ar–C), 110.8 (CN), 14.0 (SCH_3) ppm; IR (KBr): $\overline{\nu}$ = 3230 (NH), 3080 (Ar–H), 2210 (CN), 1650 (C = O), 1618 (Ar–C = N), 1590 (Ar–C = C) cm^{-1}; MS (FAB, 70 eV): *m/z* (%) = 292 ($[M+2]^+$, 38), 290 (M^+, 53).

7-Bromo-3-(methylthio)-4-oxo-4,5-dihydrofuro[3,2-*c*]quinoline-2-carbonitrile (3f, $C_{13}H_7BrN_2O_2S$) Yield: 0.167 g (50%); colorless crystals (DMF/EtOH); m.p.: 270–272 °C; R_f = 0.3 (toluene: AcOEt 5:1); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.90 (bs, 1H, NH), 8.00 (d, J = 7.7 Hz, 1H, H-9), 7.30–7.16 (m, 2H, Ar–H), 2.10 (s, 3H, SCH_3) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 163.6 (C-4), 156.8 (C-9b), 136.4 (Ar–C), 134.2, 132.0 (Ar–C), 131.8 (Ar–CH-9), 129.8 (Ar–C), 127.8 (Ar–C-Br), 126.2 (Ar–CH), 124.0, 122.1 (Ar–C), 110.2 (CN), 13.8 (SCH_3) ppm; IR (KBr): $\overline{\nu}$ = 3230 (NH), 3070 (Ar–H), 2210 (CN), 1650 (C = O), 1619 (Ar–C = N), 1590 (Ar–C = C) cm^{-1}; MS (FAB, 70 eV): *m/z* (%) = 334 ($[M-1]^+$, 20), 335 (M^+, 38), 336 ($[M+1]^+$, 52).

3-(Methylthio)-4-oxo-4,5-dihydrofuro[3,2-*c*]quinoline-2-carboxamide (4a, $C_{13}H_{10}N_2O_3S$) Yield: 0.069 g (25%); colorless crystals (EtOAc); m.p.: 340–342 °C; R_f = 0.7 (toluene: AcOEt 5:1); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.80 (bs, 1H, NH), 8.00 (dd, J = 7.7, 1.2 Hz, 1H, H-9), 7.10–6.90 (m, 5H, Ar–H, NH_2), 1.95 (s, 3H, SCH_3) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 164.0 (C-4), 158.4 ($CONH_2$), 152.0 (C-9b), 147.0 (Ar–C-amide), 136.0, 134.0 (Ar–C), 128.0, 126.4, 124.8, 124.0 (Ar–CH), 122.3, 122.0 (Ar–C), 13.1 (SCH_3) ppm; IR (KBr): $\overline{\nu}$ = 3300–3100 (NH_2, NH), 3099 (Ar–H), 1660 (C = O), 1640 (C = O), 1590 (Ar–C = C) cm^{-1}; MS (FAB, 70 eV): *m/z* (%) = 274 (M^+, 40).

8-Methyl-3-(methylthio)-4-oxo-4,5-dihydrofuro[3,2-*c*]quinoline-2-carboxamide (4b, $C_{14}H_{12}N_2O_3S$) Yield: 0.078 g (27%); colorless crystals (DMF/EtOH); m.p.: 350–352 °C; R_f = 0.65 (toluene: AcOEt 5:1); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.70 (bs, 1H, NH), 8.10 (bs, 1H, H-9), 7.15–6.92 (m, 4H, Ar–H, NH_2), 2.10 (s, 3H, CH_3), 1.85 (s, 3H, SCH_3) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 163.4 (C-4), 158.0 ($CONH_2$), 153.0 (C-9b), 146.8 (Ar–C-amide), 137.2

(Ar–C-CH_3), 136.0 (Ar–C), 132.0 (Ar–CH-9), 128.2 (Ar–CH), 128.8 (Ar–C), 126.2 (Ar–CH), 122.3, 122.0 (Ar–C), 22.0 (CH_3), 15.4 (SCH_3) ppm; IR (KBr): $\overline{\nu}$ = 3330–3150 (NH_2, NH), 3060 (Ar–H), 1665 (C = O), 1642 (C = O), 1590 (Ar–C = C) cm^{-1}; MS (FAB, 70 eV): *m/z* (%) = 288 (M^+, 34).

7-Methyl-3-(methylthio)-4-oxo-4,5-dihydrofuro[3,2-*c*]quinoline-2-carboxamide (4c, $C_{14}H_{12}N_2O_3S$) Yield: 0.074 g (26%); colorless crystals (EtOAc); m.p.: 343–345 °C; R_f = 0.6 (toluene: AcOEt 5:1); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.75 (bs, 1H, NH), 8.12 (d, J = 0.8 Hz, 1H, H-9), 7.20–7.13 (m, 4H, Ar–H, NH_2), 2.12 (s, 3H, CH_3), 1.90 (s, 3H, SCH_3) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 163.6 (C-4), 159.2 ($CONH_2$), 153.1 (C-9b), 146.8 (Ar–C-amide), 136.0 (Ar–C-CH_3), 135.8 (Ar–C), 131.4 (Ar–CH-9), 129.0 (Ar–CH), 128.8 (Ar–C), 126.2 (Ar–CH), 120.6, 119.8 (Ar–C), 22.2 (CH_3), 14.8 (SCH_3) ppm; IR (KBr): $\overline{\nu}$ = 3335–3180 (NH_2, NH), 3065 (Ar–H), 1665 (C = O), 1642 (C = O), 1580 (Ar–C = C) cm^{-1}; MS (FAB, 70 eV): *m/z* (%) = 288 (M^+, 30).

8-Chloro-3-(methylthio)-4-oxo-4,5-dihydrofuro[3,2-*c*]quinoline-2-carboxamide (4d, $C_{13}H_9ClN_2O_3S$) Yield: 0.092 g (30%); colorless crystals (DMF/EtOH); m.p.: 280–282 °C; R_f = 0.35 (toluene: AcOEt 5:1); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.90 (bs, 1H, NH), 7.80 (d, J = 0.8 Hz, 1H, H-9), 7.20–7.16 (m, 4H, Ar–H, NH_2), 1.90 (s, 3H, SCH_3) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 164.2 (C-4), 159.5 ($CONH_2$), 154.0 (C-9b), 146.2 (Ar–C-amide), 135.0, 133.4, 130.0 (Ar–C), 129.8 (Ar–CH-9), 128.8 (Ar–C-Cl), 127.0 (Ar–CH), 125.8 (Ar–C), 124.0 (Ar–CH), 15.8 (SCH_3) ppm; IR (KBr): $\overline{\nu}$ = 3295–3180 (NH_2, NH), 3070 (Ar–H), 1662 (C = O), 1650 (C = O), 1590 (Ar–C = C) cm^{-1}; MS (FAB, 70 eV): *m/z* (%) = 308 (M^+, 28), 309 ($[M+1]^+$, 7), 310 ($[M+2]^+$, 5).

7-Chloro-3-(methylthio)-4-oxo-4,5-dihydrofuro[3,2-*c*]quinoline-2-carboxamide (4e, $C_{13}H_9ClN_2O_3S$) Yield: 0.0910 g (29%); colorless crystals (DMF/EtOH); m.p.: 263–265 °C (decmp); R_f = 0.5 (toluene: AcOEt 5:1); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.95 (bs, 1H, NH), 7.80 (dd, J = 1.2, 0.8 Hz, 1H, H-9), 7.10–6.96 (m, 4H, Ar–H, NH_2), 1.98 (s, 3H, SCH_3) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 165.0 (C-4), 158.0 ($CONH_2$), 153.2 (C-9b), 146.8 (Ar–C-amide), 136.0, 134.4, 131.0 (Ar–C), 128.9 (Ar–CH-9), 127.8 (Ar–C-Cl), 126.0 (Ar–CH), 124.6 (Ar–C), 122.0 (Ar–CH), 15.9 (SCH_3) ppm; IR (KBr): $\overline{\nu}$ = 3290–3190 (NH_2, NH), 3080 (Ar–H), 1665 (CO), 1640 (C = O), 1590 (Ar–C = C) cm^{-1}; MS (FAB, 70 eV): *m/z* (%) = 310 ($[M+2]^+$, 10), 308 (M^+, 40).

8-Bromo-3-(methylthio)-4-oxo-4,5-dihydrofuro[3,2-*c*]quinoline-2-carboxamide (4f, $C_{13}H_9BrN_2O_3S$) Yield: 0.116 g (33%); colorless crystals (DMF/H_2O); m.p.: 267–269 °C (decomp); R_f = 0.4 (toluene: AcOEt 5:1); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.80 (bs, 1H, NH), 7.70 (d, J = 0.7 Hz, 1H, H-9), 7.22–7.18 (m, 4H, Ar–H, NH_2), 1.94 (s, 3H, SCH_3) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 165.0 (C-4), 157.0 ($CONH_2$), 154.0 (C-9b), 147.8 (Ar–C-amide), 135.4, 134.0, 132.6 (Ar–C), 131.4 (Ar–C-Cl), 128.8 (Ar–CH-9), 127.0 (Ar–CH), 125.8 (Ar–C), 123.6 (Ar–CH), 15.8 (SCH_3) ppm; IR (KBr): $\overline{\nu}$ = 3180–3290 (NH_2, NH), 3060 (Ar–H), 1660 (C = O), 1652 (C = O), 1590 (Ar–C = C) cm^{-1}; MS (FAB, 70 eV): *m/z* (%) = 352 ($[M-1]^+$, 18) 351 ($[M-2]^+$, 10).

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