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Reinvestigation of bromination of 8-substituted quinolines and synthesis of novel phthalonitriles

Salih Ökten^{*1}, Osman Çakmak², Aisha Saddiqa³, Bahadır Keskin⁴,
Seda Özdemir⁵ and Merve İnal^{4,5}

¹ Department of Mathematic and Science Education, Faculty of Education, Kırıkkale University, 71450, Yahşihan, Kırıkkale, Türkiye

² Department of Nutrition and Dietetics, School of Health Sciences, İstanbul Gelişim University, 34315 Avcılar, İstanbul, Türkiye

³ Department of Chemistry, Faculty of Natural Sciences, Government College Women University, 51310, Sialkot, Pakistan

⁴ Department of Chemistry, Faculty of Art and Science, Yıldız Technical University, 34210, Davutpaşa, İstanbul, Türkiye

⁵ Department of Chemistry, Faculty of Art and Science, Gaziosmanpaşa University, 60240, Tokat, Türkiye

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Abstract: Bromination of a series of 8-substituted quinolines was reinvestigated and specified for optimum yields and isolation conditions. Mono bromination of 8-hydroxyquinoline (**2a**) and 8-aminoquinoline (**2c**) gave mixture of mono and dibromo derivatives 5,7-dibromo-8-hydroxyquinoline (**3a**), 5,7-dibromo-8-aminoquinoline (**3c**), 7-bromo-8-hydroxyquinoline (**3d**), 5-bromo-8-aminoquinoline (**3e**) while 8-methoxyquinoline (**2b**) furnished 5-bromo-8-methoxyquinoline (**3f**) as sole product. Novel phthalonitriles, 4-(quinolin-8-yloxy)phthalonitrile (**6**) and 4-chloro-5-(quinolin-8-yloxy)phthalonitrile (**8**) of 8-hydroxyquinoline (**2a**) were synthesized and converted into their respective bromo derivatives 4-(5-bromoquinolin-8-yloxy)phthalonitrile (**7**) and 4-((5-bromoquinolin-8-yl)oxy)-5-chlorophthalonitrile (**9**).

Keywords: Bromination; hydroxyquinoline; phthalonitrile; methoxyquinoline; aminoquinoline. © 2016 ACG Publications. All rights reserved.

1. Introduction

In drug design, quinoline (**1**) and its derivatives are a very important class of *N*-heterocyclic compounds. Quinoline (**1**) and the compounds containing the quinoline scaffold are considered as targets for the development of synthetic strategies and evaluation of biological activities.

This class of aromatic compounds has a wide spectrum of biological activities, including antimalarial,¹ antimicrobial,² antibacterial,³ antiparasitic,⁴ and anticancer⁵⁻⁶ activities. Due to the indispensable role of quinoline and its derivatives in pharmaceutical chemistry, a number of protocols

* Corresponding Author: E-Mail: sokten@gmail.com . Phone: + 90318 3574242/ 1394-1357

were established for their synthesis, especially 8-substituted quinolines **2a-c** (Figure 1), such as hydroxy-, methoxy-, amino-, and halogen-substituted quinolines.

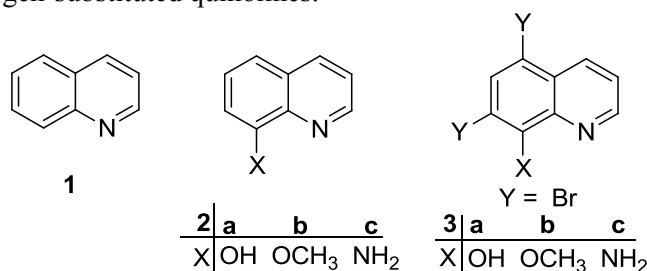


Figure 1. Structures of quinoline and 8-substituted quinolines.

Selective bromination of organic molecules, especially aromatics, has gained significant commercial importance in the last few decades. Bromoquinolines have become important tools for chemists as precursors for carbon-carbon bond formation to afford novel substituted quinoline derivatives with potential applications in the pharmaceutical and material industries.⁶⁻⁷ On the molecular design level, different substituents were introduced at position C-8 of the quinoline nucleus with alterations in their conformational/physicochemical parameters, specifically varied between flexible, semi-flexible, rigid, hydrophilic, hydrophobic, hydrogen bond-donating, and/or hydrogen bond-accepting characteristics.⁸ Since the pyridine ring is electron-deficient, direct halogenation of quinolines rarely takes place on the pyridine motif of quinoline unless it is substituted with strong electron donating groups. Therefore, direct halogenation of quinolines generally occurs at the benzene moiety; NBS and Br₂ have been commonly used as halogenation reagents.^{7,9}

Although many experimental works have examined the bromination of these derivatives, it still remains an area of active research. This study demonstrated that bromination of 8-OH **2a**, -MeO **2b**, and -NH₂ **2c** substituted quinolines is complicated. A huge number of studies examined the bromination of 8-hydroxyquinoline (8-OHQ, **2a**). In the initial reports,¹⁰⁻¹¹ bromination of 8-hydroxyquinoline (**2a**) afforded 5-bromo and 5,7-dibromo derivatives. Multiple groups worked toward obtaining optimum yields of 5-bromo-8-hydroxyquinoline. The treatment of 8-OHQ **2a** with molecular bromine in the presence of H₂SO₄ at low temperature (-10 °C) was furnished 5-bromo (52%) and 5,7-dibromo (19%) **3a** derivatives; if the temperature was raised to -5 °C, 5-bromo-8-quinolinol was produced as single product (57%), whereas 5,7-dibromide **3a** was formed as a single product at 15 °C.¹²

Many groups have formed 5,7-dibromo-8-hydroxyquinoline **3a** by treating 8-hydroxyquinoline with molecular bromine in the presence of variety of solvents, such as EtOH,¹⁰ H₂O,¹³ dilute H₂SO₄,¹⁴ and HCl.¹⁵⁻¹⁶ 7-Bromo-8-hydroxyquinoline (**3d**) was obtained as the sole product (92%) of direct bromination of **2a** in a mixture of dry toluene and *t*-butylamine at -75 °C.⁹ The treatment of **2a** with different amounts of NBS yielded **3a** as the main product, and 5-bromo-8-hydroxyquinoline as a lesser product.¹⁷⁻¹⁸ Recently, iso-amyl nitrite/HBr¹⁹ and *aq.* CaBr₂-Br₂,²⁰ an excellent, environmentally-friendly and recyclable brominating agent, were used to generate 5,7-dibromo-8-hydroxyquinoline (**3a**). Ionic liquid 1,3-di-*n*-butylimidazoliumtribromide ([BBIm]Br₃) was reported as an efficient monobrominating agent for different aromatic systems to yield 5-bromo-8-hydroxyquinoline.²¹ Bromination of 8-hydroxyquinoline **2a** in AcOH afforded dibromide **3a** in yield of 75%.²²

Electrophilic halogenation of 8-methoxyquinoline (**2b**) with molecular bromine and NBS was studied in various solvents (H₂SO₄; acetic acid, glacial; chloroform; pyridine; diethylamine; NaOH, 10%) and compared with that of 8-quinolinol (**2a**). The bromination of 1 equivalent of 8-methoxyquinoline (**2b**) with 2 and 3 equivalents of NBS in 93% sulfuric acid was also complicated by the appearance of side products; in the presence of 2 equivalents of NBS, 5-bromo-8-methoxyquinoline (**3f**) (10%) and 5,7-dibromo-8-methoxyquinoline (**3b**) (30%) were extracted from the reaction mixture along with two other unwanted brominated products, whereas 3 equivalents of NBS yielded **3b** as the major product (57%).²³

8-Aminoquinoline (**2c**) was treated with 2 equivalents of Br₂; 5,7-dibromo-8-aminoquinoline (**3c**) was then obtained in a quantitative yield.²⁴ Bromination of **2c** with 1 equivalent of NBS in acetonitrile afforded 5-bromo-8-aminoquinoline **3e**.²⁵ Moreover, bromination of 8-aminoquinoline with NBS in the

presence of a solid composite ($\text{LiClO}_4\text{-SiO}_2$)²⁶⁻²⁷ and Br_2 in AcOH ²⁸ yielded 5,7-dibromo-8-aminoquinoline **3c** in quantitative yields.

In this study, both to compare the selectivity difference on bromination of 8-substituted quinolines (**2a-c**) and phthalonitriles derived (**6, 8**) from 8-OHQ **2a**, we reinvestigated the bromination of several 8-substituted quinoline derivatives (**2a-c**) and synthesized new phthalonitriles (**6-9**).

2. Experimental

All the reagents and solvents for synthesis were commercially available. Thin layer chromatography was carried out on Merck silica F_{254} 0.255-mm plates, and spots were visualized by UV fluorescence at 254 nm. Classic column chromatography was performed using Merck 60 (70-230 mesh) silica gel. Melting points were determined on a Thomas-Hoover capillary melting point apparatus. Solvents were concentrated at reduced pressure. NMR spectra were recorded on a Bruker 400 MHz for ^1H -NMR and at 100 MHz for ^{13}C -NMR. IR spectra were recorded on a JASCO 430 FT/IR instrument. Elemental analysis was recorded on an ElementarVario MICRO Cube instrument.

3.1. Bromination of 8-hydroxyquinoline (**2a**, 1.5 eq):

A solution of bromine (2.202 g, 13.8 mmol, 1.5 eq) in CH_3CN (10 mL) was added to a solution of 8-hydroxyquinoline (**2a**) (1 g, 6.9 mmol) in CH_3CN (20 mL) over 10 min. The mixture was stirred in a fridge (0 °C) for 1 day. During reaction, quinoline salt was formed due to HBr. After completely consumption of bromine, the resulting yellow solid was dissolved in CH_3CN (15 mL). The organic layer was washed with 5% NaHCO_3 solution (4 $\times$ 25 mL) and dried over Na_2SO_4 . After evaporation of the solvent under reduced pressure, NMR analysis of the residue (2.87 g) showed the formation of 5,7-dibromo-8-hydroxyquinoline (**3a**) and 7-bromo-8-hydroxyquinoline (**3d**). A small amount (1.8 g) of the mixture of products was added to CH_3CN (10 mL). The crude mixture was dissolved in CH_3CN (15 mL) and filtered; the soluble filtrate was crystallized in CH_3CN and dibromide **3a** was isolated as yellow needles (37% isolated yield, 0.77 g). The insoluble solid was dissolved in a mixture of methanol and acetone (1/1) overnight. Monobromide **3d** was recrystallized using a mixture of methanol and acetone (1/1) (51% isolated yield, 0.78 g).

7-bromo-8-hydroxyquinoline (**3d**):

Yield: 51%; M.p. 138-139 °C (Lit³¹ 139 °C); ^1H NMR (400 MHz, CDCl_3) (δ /ppm): 8.83 (dd, J_{23} = 4.4 Hz 1H, H-2, J_{24} = 1.6 Hz), 8.51 (dd, 1H, H-4, J_{42} = 1.2 Hz, J_{43} = 8.4 Hz), 7.73 (d, 1H, H-6, J_{65} = 8.4 Hz), 7.59 (dd, 1H, H-3, J_{32} = 4.4 Hz, J_{34} = 8.4 Hz), 7.10 (d1 H, H-5, J_{56} = 8.4 Hz), 3.3 (s, 1H, -OH).

3.2. Synthesis of 5,7-dibromo-8-hydroxyquinoline (**3a**):

A solution of bromine (0.67 g, 4.20 mmol) in CHCl_3 (5 mL) was added to a solution of 8-hydroxyquinoline (**2a**) (0.3 g, 2.06 mmol) in CHCl_3 (10 mL) over 5 min. The mixture was stirred at room temperature for 1 h. The resulting yellow solid was dissolved in CHCl_3 (15 mL), washed with 5% NaHCO_3 (3 $\times$ 15 mL), and dried over Na_2SO_4 . After evaporation of the solvent, NMR analysis of the residue (0.56 g) showed the formation of 5,7-dibromo-8-hydroxyquinoline (**3a**) as sole product. The product was crystallized in benzene in 90% yield.

5,7-Dibromo-8-hydroxyquinoline (**3a**):

Yellow needle crystals, yield: 90%; M.p. 196-198 °C (Lit²², 198-199 °C); ^1H NMR (400 MHz, CDCl_3) (δ /ppm): 8.89 (dd, J_{23} = 4.4 Hz, J_{24} = 1.2 Hz, 1H, H-2), 8.54 (dd, J_{42} = 1.2 Hz, J_{43} = 8.4 Hz, 1H, H-4), 7.96 (s, 1H, H-5), 7.65 (dd, J_{32} = 4.4 Hz, J_{34} = 8.4 Hz, 1H, H-3), 3.3 (s, 1H, -OH); ^{13}C NMR (100 MHz,

CDCl₃) (δ/ppm): 149.7, 148.9, 138.6, 136.9, 134.1, 126.8, 123.0, 110.3, 104.8; IR (ν/cm⁻¹): 3066, 2921, 1581, 1563, 1490, 1457, 1396, 1365, 1332, 1270, 1201, 1133, 933, 871, 806, 784, 723, 649.

3.3. Synthesis of 5-bromo-8-methoxyquinoline (**3f**):

A solution of bromine (422.4 mg, 2.7 mmol, 1.1 eq) in CHCl₃ was added dropwise to 8-methoxyquinoline (**2b**) (382.4 mg, 2.4 mmol) in distilled CH₂Cl₂ (15 mL) over 10 min in the dark at ambient temperature and stirred for 2 days. The course of reaction was monitored by TLC; after completion of the reaction, the organic layer was washed with 5% NaHCO₃ (3 × 20 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The crude material (560 mg) was passed through a short alumina column, eluting with AcOEt/hexane (1:3, 150 mL). After evaporating the solvent, a brown solid of **3f** was obtained (535 mg, 92% yield).

5-bromo-8-methoxyquinoline (**3f**):

Brown solid, yield: 92%; M.p. 80-82 °C (Lit³², 86 °C; Lit³⁵, 88 °C; Lit³⁶, 82 °C); ¹H NMR (400 MHz, CDCl₃) (δ/ppm): 8.89 8.91 (dd, 1H, H-2, *J*₂₃ = 4.0 Hz, *J*₂₄ = 1.2 Hz), 8.43 (dd, 1H, H-4, *J*₄₃ = 8.4 Hz, *J*₄₂ = 1.6 Hz), 7.66 (d, 1H, H-6, *J*₆₇ = 8.4 Hz), 7.49 (dd, 1H, H-3, *J*₃₂ = 4.0 Hz, *J*₃₄ = 8.4 Hz), 6.87 (d, 1H, H-7, *J*₇₆ = 8.4 Hz), 4.04 (s, OCH₃); ¹³C NMR (100 MHz, CDCl₃) (δ/ppm): 152.2, 149.7, 140.8, 135.5, 130.0, 128.1, 122.8, 111.8, 108.1, 56.2 (OCH₃); IR (ν/cm⁻¹): 2915, 2848, 1600, 1588, 1500, 1460, 1352, 1300.

3.4. Synthesis of 5,7-dibromo-8-methoxyquinoline (**3b**):

5,7-dibromoquinolin-8-ol (**3a**) (1.0 g, 3.3 mmol) was added to a solution of NaOH (132 mg, 3.3 mmol) in distilled water (100 mL). Me₂SO₄ (416 mg, 3.3 mmol) was added dropwise to the mixture at -10 °C for 1 h while being stirred. The mixture was heated to 70-80 °C for 1 h. After completion of the reaction (the color of the mixture changed, 2 h), the solid was dissolved in CHCl₃ (50 mL). The organic layer was successively washed with 10% Na₂CO₃ (2 x 15 mL) and 10% NaOH (2 x 15 mL), dried over Na₂SO₄, and the solvent was removed under vacuum. The crude material (2.12 g) was passed through a short alumina column and eluted with EtOAc–hexane (1:6, 150 mL). The white needles **3b** (1 g, 95%) were obtained at room temperature.

5,7-Dibromo-8-methoxyquinoline (**3b**):

White needles, M.p. 99-102 °C (Lit³², 103 °C; Lit³⁶, 99 °C); ¹H NMR (400 MHz, CDCl₃) (δ/ppm): 9.00 (dd, *J*₂₃ = 3.2 Hz, *J*₂₄ = 1.6 Hz, 1H, H-2), 8.52 (dd, 1H, H-4, *J*₄₃ = 8 Hz, *J*₄₂ = 1.6 Hz), 8.02 (s, 1H, H-6), 7.58 (dd, 1H, H-3, *J*₃₄ = 8.4 Hz, *J*₃₂ = 3.2 Hz), 4.19 (s, 3H, OCH₃); ¹³C NMR (100 MHz, CDCl₃) (δ/ppm): 153.3, 150.9, 143.8, 136.1, 133.7, 128.3, 122.5, 116.3, 116.5, 62.1 (OCH₃); IR (ν/cm⁻¹): 2919, 2850, 1733, 1600, 1578, 1490, 1462, 1383, 1370, 1353, 1086 (Lit³²).

3.5. Bromination of 8-aminoquinoline (**2c**, 1.5 eq Br₂):

A solution of bromine (168 mg, 1.05 mmol, 1.5 eq) in CHCl₃ was added dropwise to a solution of 8-aminoquinoline (**2c**, 100 mg, 0.7 mmol) in distilled CH₂Cl₂ (2 mL) over 10 min in the dark at room temperature. After completion of the reaction (complete consumption of bromine, 17 h), the organic layer was washed with 5% NaHCO₃ solution (3 × 20 mL) and dried over Na₂SO₄. After evaporation of the solvent, the crude material (0.185 mg) was passed through a short alumina column and eluted with AcOEt/hexane (1:6, 173 mL). After evaporation of the solvent, NMR analysis of the residue indicated the formation of 5,7-dibromo-8-aminoquinoline (**3c**) and 5-bromo-8-aminoquinoline (**3e**) in a ratio of 42:58, respectively. Due to the very close R_f values of 5,7-dibromo-8-aminoquinoline (**3c**) and 5-bromo-8-aminoquinoline (**3e**) were not isolated as sole product.

5-bromo-8-aminoquinoline (3e):

¹H NMR (400 MHz, CDCl₃) (δ/ppm): 8.78 (dd, 1H, H-2, J_{23} = 4.0 Hz, J_{24} = 1.2 Hz), 8.44 (dd, 1H, H-4, J_{42} = 1.2 Hz, J_{43} = 8.4 Hz), 7.60 (d, 1H, H-6, J_{67} = 8.0 Hz), 7.52 (dd, 1H, H-3, J_{32} = 4.0 Hz, J_{34} = 8.4 Hz), 6.83 (d, 1H, H-7, J_{76} = 8.0 Hz), 5.07 (bs, 2H, NH₂).

3.6. Synthesis of 5,7-dibromo-8-aminoquinoline (3c):

A solution of bromine (0.222 mg, 1.42 mmol, 2.1 eq) in CHCl₃ was added dropwise to 8-aminoquinoline (**2c**) (100 mg, 0.7 mmol) in distilled CH₂Cl₂ (2 mL) over 10 min in the dark and at room temperature. After completion of the reaction (complete consumption of bromine, 17 h), the organic layer was washed with 5% NaHCO₃ solution (3 × 20 mL) and dried over Na₂SO₄. After evaporation of the solvent, the crude material (215 mg) was passed through a short alumina column and eluted with AcOEt/hexane (1:6, 150 mL). After evaporating the solvent, a brown solid product **3c** was obtained (208 mg, 99% yield).

5,7-Dibromo-8-aminoquinoline (3c):

Brown solid, yield: 99%; M.p. 118-120 °C (Lit²⁸, 119-122 °C); ¹H NMR (400 MHz, CDCl₃) (δ/ppm): 8.77(dd, 1H, H-2, J_{23} = 4.0 Hz, J_{24} = 1.2 Hz), 8.40 (dd, 1H, H-4, J_{42} = 1.2 Hz, J_{43} = 8.4 Hz), 7.80 (s, 1H, H-6), 7.51 (dd, 1H, H-3, J_{32} = 4.4 Hz, J_{34} = 8.4 Hz) 5.48 (bs, 2H, NH₂); ¹³C NMR (100 MHz, CDCl₃) (δ/ppm): 148.4, 142.1, 138.4, 135.7, 133.2, 126.7, 122.5, 106.9, 103.2.

3.7. Synthesis of 4-(quinolin-8-yloxy)phthalonitrile (6):

4-Nitrophthalonitrile (237 mg, 1.37 mmol) and 8-hydroxyquinoline (**2a**) (200 mg, 6.90 mmol) were dissolved successively in dry dimethylformamide (DMF) (8 mL) at room temperature. The reaction mixture was heated to 50 °C for 24 h under N₂ atmosphere, while anhydrous K₂CO₃ (2.38 g, 17.25 mmol) was added to the reaction solution in 4 portions every 30 min. Afterward, the reaction mixture was cooled to room temperature and poured into ice water (100 mL). After filtration under vacuum, the crude product was crystallized from ethanol-water (1:1) to get pure product **6** (0.233 g, 62%).

4-(quinolin-8-yloxy)phthalonitrile (6):

Pale-yellow solid, yield: 62%; M.p. 196-197 °C; ¹H NMR (500 MHz, CDCl₃) (δ/ppm): 8.86 (dd, 1H, H-2, J_{23} = 4.2 Hz, J_{23} = 1.6 Hz), 8.29 (dd, 1H, H-4, J_{43} = 8.4 Hz, J_{42} = 1.5 Hz), 7.85 (dd, 1H, H-5, J_{56} = 8.2 Hz, J_{57} = 1.1 Hz), 7.71 (d, 1H, H-6', $J_{6'5'}$ = 8.4 Hz), 7.63 (t, 1H, H-6, J_{65} = 8.1 Hz), 7.50–7.53 (m, 2H, H-7, H-3), 7.27 (dd, 1H, H-5', $J_{5'6'}$ = 8.8 Hz, $J_{5'3'}$ = 2.6 Hz), 7.19 (d, 1H, H-3, $J_{3'5'}$ = 2.6 Hz); ¹³C NMR (125 MHz, CDCl₃) (δ/ppm): 162.5, 150.9, 149.1, 140.8, 136.6, 135.2, 130.3, 126.8, 126.6, 122.4, 121.4, 121.2, 121.0, 117.4, 115.6, 115.2, 108.6; FT-IR (ν/cm⁻¹): 3087–3022 (Ar-H), 2950, 2923, 2232 (C≡N), 1599 (Ar C=C), 1483, 1463, 1410, 1384, 1277, 1250, 1162, 1111 (Ar-O-Ar), 1084, 1059, 1035, 974, 910, 843, 757; Analysis (% Calculated/found) for C₁₇H₉BrN₃O (*m/z*: 271.27) C: 75.27/75.19, H: 3.34/3.36, N: 15.49/15.40.

3.8. Synthesis of 4-(5-bromoquinolin-8-yloxy)phthalonitrile (7):

The solution of 4-(quinolin-8-yloxy)phthalonitrile (**6**) (100 mg, 0.3686 mmol) in CH₃CN (10 mL) was cooled to 0 °C. The device for absorbing the evolved hydrogen bromide was attached to the reaction flask. The drying tube, which was attached to the reaction apparatus, was filled with CaCl₂ (inside) to absorb released HBr. To the solution, which was protected from light, a solution of bromine (59 mg, 0.3686 mmol) in CH₃CN (3 mL) was added dropwise over 15 min. HBr was evacuated during the reaction. Reaction progress was monitored by TLC. After the bromination was completed (34 h), water was added to the reaction and the resulting yellow-green solid was dissolved in diethyl ether (20 mL).

The organic layer was washed with 10% Na₂CO₃ solution (3 × 10 mL) and dried over Na₂SO₄. After evaporation of the solvent, the pure colorless compound **7** was further purified by chromatography over a silica gel column using EtOAc/hexane (1:3) as eluent and obtained yellow solid **7** in yield of 52% (0.068 g).

4-(5-bromoquinolin-8-yloxy)phthalonitrile (**7**):

Yellow solid, yield: 52%; M.p. 218-219 °C; ¹H NMR (500 MHz, CDCl₃): (δ/ppm): 8.89 (dd, *J*₂₃ = 4.1 Hz, *J*₂₄ = 1.5 Hz, 1H, H-2), 8.67 (dd, *J*₄₃ = 8.6 Hz, *J*₄₂ = 1.5 Hz, 1H, H-4), 8.10 (d, 1H, H-6, *J*₆₇ = 8.2 Hz), 8.00 (d, 1H, H-6', *J*_{6'5'} = 8.8 Hz), 7.78 (dd, 1H, H-3, *J*₃₂ = 4.2 Hz, *J*₃₄ = 8.6 Hz), 7.71 (d, 1H, H-7, *J*₇₆ = 8.2 Hz), 7.64 (d, 1H, H-3', *J*_{3'5'} = 2.6 Hz), 7.45 (dd, 1H, H-5', *J*_{5'6'} = 8.8 Hz, *J*_{5'3'} = 2.6 Hz); ¹³C NMR (125 MHz, CDCl₃): (δ/ppm): 162.2, 151.4, 148.9, 141.5, 136.3, 135.3, 130.3, 129.4, 123.5, 121.5, 121.3, 121.2, 119.7, 117.5, 115.5, 115.0, 108.9; FT-IR (ν/cm⁻¹): 3099–3041 (Ar–H), 2947, 2921, 2227 (C≡N), 1597, 1564 (Ar C=C), 1482, 1466, 1421, 1386, 1279, 1243, 1196, 1166, 1136 (Ar–O–Ar), 1093, 946, 880, 831, 795; Analysis (% Calculated/found) for C₁₇H₈BrN₃O (*m/z*: 348.99) C: 58.31/58.47, H: 2.30/2.30, N: 12.00/11.86.

3.9. Synthesis of 4-chloro-5-(quinolin-8-yloxy)phthalonitrile (**8**):

8-Quinolinol (**2a**) (0.360 g, 2.45 mmol) and 4,5-dichlorophthalonitrile (0.407 g, 2.07 mmol) were dissolved in dry dimethyl formamide (20 mL). After stirring for 30 min at room temperature, dry, fine-powdered potassium carbonate (0.856 g, 6.20 mmol) was added portion-wise over 2 h with vigorous stirring. The reaction was stirred for 24 h at room temperature and poured into ice water (150 g). The product was filtered off and washed with water until the filtrate was neutral. Recrystallization from ethanol gave a light-yellow product **8** (0.596 g, 94%).

5-chloro-4-(quinolin-8-yloxy)phthalonitrile (**8**):

Pale yellow solid, yield: 94%; M.p. 203 °C (decomposed); ¹H NMR (500 MHz, CDCl₃): (δ/ppm): 8.84 (dd, 1H, H-2, *J*₂₃ = 4.2 Hz, *J*₂₄ = 1.5 Hz), 8.29 (dd, 1H, H-4, *J*₄₃ = 8.5 Hz, *J*₄₂ = 1.5 Hz), 7.92 (s, 1H, H-3'), 7.88 (d, 1H, H-5, *J*₅₆ = 8.1 Hz), 7.64 (t, 1H, H-6, *J*₆₅ = 8.1 Hz), 7.55-7.51 (m, 2H, H-7, H-3), 6.78 (s, 1H, H-6'); ¹³C NMR (125 MHz, CDCl₃): (δ/ppm): 158.8, 151.2, 148.9, 140.4, 136.5, 135.4, 130.3, 128.9, 127.0, 126.8, 122.5, 121.0, 120.7, 115.0, 114.7, 114.6, 109.2; FT-IR (ν/cm⁻¹): 3098–3045 (Ar–H), 2953, 2914, 2227 (C≡N), 1588, 1551 (Ar C=C), 1487, 1468, 1383, 1283, 1256, 1232, 1160, 1131 (Ar–O–Ar), 1081, 1007, 886, 832, 799; Analysis (% Calculated/found) for C₁₇H₈ClN₃O (*m/z*: 305.72) C: 66.79/67.01, H: 2.64/2.67, N: 13.74/13.58.

3.10. Synthesis of 4-((5-bromoquinolin-8-yl)oxy)-5-chlorophthalonitrile (**9**):

A solution of 4-chloro-5-(quinolin-8-yloxy)phthalonitrile (**8**) (100 mg, 0.32 moles, 1eq) was dissolved in 5 mL of CH₃CN. The apparatus was equipped with dropping funnel and a guard tube with CaCl₂ (as HBr absorber). The bromine (104 mg, 0.65 mmol, 2 eq, dissolved in 2 mL of CH₃CN) was added dropwise via dropping funnel at room temperature during the period of 10 min. The mixture was allowed to stir overnight at room temperature. The reaction mixture was poured on to 5% solution of Na₂CO₃ (10 mL) and filtered. The solid was washed with distilled water (15 mL), dissolved on AcOEt (20 mL), dried with anhydrous Na₂SO₄. After evaporation of the solvent, the pure colorless compound **9** was further purified by chromatography over a silica gel column using AcOEt/hexane (7:3, *R*_f: 0.6) as eluent and obtained **9** (80 mg, 64%).

4-((5-bromoquinolin-8-yl)oxy)-5-chlorophthalonitrile (**9**):

White solid, yield: 64%; M.p. 212 °C (decomposed); ¹H NMR (500 MHz, CDCl₃): (δ/ppm): 8.78 (dd, 1H, H-2, *J*₂₃ = 4.0 Hz, *J*₂₄ = 1.5 Hz), 8.57 (dd, 1H, H-4, *J*₄₃ = 8.5 Hz, *J*₄₂ = 1.5 Hz), 7.86 (m, 2H, H-6,

H-3'), 7.55 (dd, 1H, H-3, $J_{32} = 4.0$ Hz, $J_{34} = 8.5$ Hz), 7.36 (d, 1H, H-7, $J_{76} = 8.0$ Hz), 6.73 (s, 1H, H-6"); ^{13}C NMR (125 MHz, CDCl_3) (δ /ppm): 158.4, 151.6, 148.7, 141.0, 136.4, 135.5, 130.3, 129.5, 129.1, 123.6, 121.3, 120.7, 120.1, 115.1, 114.5, 114.4, 109.7; FT-IR (ν/cm^{-1}): 3084–3018 (Ar–H), 2227 ($\text{C}\equiv\text{N}$), 1588, 1551 (Ar C=C), 1487, 1468, 1383, 1283, 1256, 1232, 1160, 1131 (Ar–O–Ar), 1081, 1007, 886, 832, 799; Analysis (% Calculated/found) for $\text{C}_{17}\text{H}_7\text{ClBrN}_3\text{O}$ (m/z : 384.61) C: 53.09/52.88, H: 1.83/1.79, N: 10.93/11.04.

3. Results and Discussion

In our approach for the bromination of 8-substituted quinoline derivatives, we reinvestigated a synthetic route that 8-substituted quinolines (OH, OCH_3 , NH_2) were treated with molecular bromine in mild conditions. We worked to optimize the conditions for the bromination of 8-substituted quinolines **2a–c** to generate their mono and dibromo derivatives (**3a–f**). Whereas quinoline **1** initially reacted with bromine to produce bromine salt **4**,^{7,29} the bromination of 8-substituted quinoline (OH, OCH_3 , NH_2) under several sets of reaction conditions accomplished their mono- and di-bromo derivatives, **3a** and **3c–f**, with variable ratios, depending on the equivalents of Br_2 used in the reaction (Figure 1).

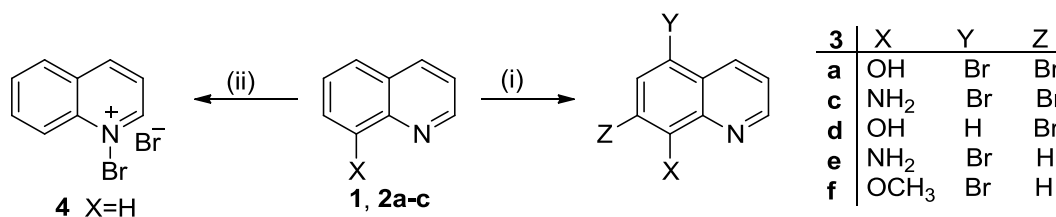


Figure 1. Bromination of 8-substituted quinolines. Reagents and conditions. (i) Br_2 (1.1–2.1 eq), ($\text{CH}_3\text{CN}/\text{CH}_2\text{Cl}_2$), 0 °C–24 °C, 1–4 days; (ii) Br_2 (1.1 eq), (CCl_4), 24 °C.

Though many studies have reported the bromination of 8-hydroxyquinoline (**2a**) under different conditions, the reaction conditions were not optimized to realize the selective bromination of **2a**. We attempted to set the condition for selective synthesis of **3a** and **3d** by treating molecular bromine with 8-quinolinol (**2a**) in CH_3CN at 0 °C (Table 1, Entries 1–5). In the literature, AcOH ²¹ and MeOH ²⁸ were used as solvents for the synthesis of **3a** with moderate yields (75% and 69%, respectively). It was observed that 2.1 equivalents of bromine afforded **3a** in yield of 90% with 100% conversion of **2a**, regardless of the solvent; however, less than 2.1 equivalents of Br_2 furnished the mixture of **3a** and **3d** and the conversion rate depended on the solvent of choice (Table 1, Entries 1, 3, and 4). The attempt to adjust the conditions to obtain **3d** as the sole product failed, but its maximum yield (58%) was obtained with 1.5 equivalents of bromine (Table 1, Entry 3).

The synthesized compounds **3a** and **3d** were isolated physically by differences in solubility. The dibromide **3a** is fairly soluble in acetonitrile, acetone, ethylacetate, chloroform, dichloromethane, benzene, toluene, and hexane, whereas compound **3d** is insoluble in these solvents. However, **3d** was marginally solved in the mixture of methanol and acetone during a period of 8 h.

The NMR spectral data of **3a** confirmed the reported values²² but disagreed with the values reported in another study,³⁰ indicating that the latter data could be wrongly recorded. The crystal structure and ^1H NMR values of **3d** were reported,³¹ but the ^1H NMR values of **3d** reported by Collis *et al.* (2003) did not match ours, especially the chemical shift of H-4 that we observed (δ_{H} 8.51, versus Collis *et al.*'s δ_{H} 8.15); Collis *et al.* may have made errors in recording these values. The ^1H NMR spectrum of **3d** we recorded is available in the supporting material.

To compare reactivity and selectivity, 8-aminoquinoline (**2c**) and 8-methoxyquinoline (**2b**) were subjected to the bromination at conditions of **2a**. 8-Aminoquinoline (**2c**), synthesized by the reduction of

8-nitroquinoline **5** with iron powder in high yield (99%), was reacted with 1.5 and 2 equivalents of bromine at ambient temperature (Figure 2, Table 1, Entries 9, 10). 8-Aminoquinoline **2c** was completely transformed into 5,7-dibromo-8-aminoquinoline (**3c**) (99%) with 2 equivalents of bromine, while 1.5 equivalents of bromine resulted in the formation of an inseparable mixture (due to close *R_f*) of **3c** and **3e** with a product ratio of 42:58 (Figure 2, Table 1, Entry 9). Spectral data (NMR and IR) of **3c** and **3e** were confirmed by the literature.^{25,28}

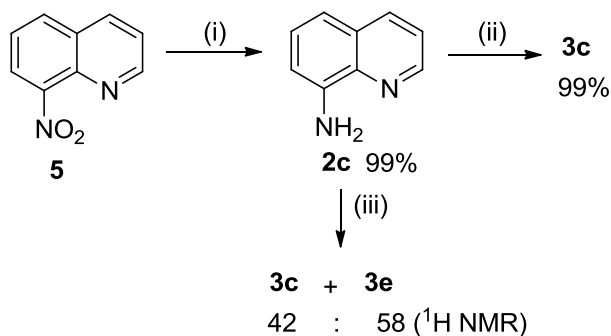


Figure 2. Reagents and conditions. (i) Fe (6 eq), AcOH, 70-80 °C, 2 h; (ii) Br₂ (2 eq), CH₂Cl₂, rt, 17 h; (iii) Br₂ (1.5 eq), CH₂Cl₂, rt, 17 h.

The bromination of 8-methoxyquinoline (8-MeOQ, **2b**) was repeated with variable equivalents of Br₂, as depicted in Table 1 (Entries 6-7) and **3f** was obtained in each case as a single product (92%). 8-MeOQ **2b** showed regioselective bromination at the C-5 position of **2b**. In the ¹H NMR spectrum of **3f**, the characteristic doublet for H-2 of the quinoline scaffold was observed at δ_H 8.91 ppm in ¹H NMR. Protons of the benzene ring of **3f** gave an AB signal system (*J*_{6,7} = 8.4 Hz), assigning bromine to C-5. In the literature,²⁷ 5-bromo-8-quinolinol (**3d**) was treated with MeI in the presence of K₂CO₃ in acetone to get **3f**; **3f** was characterized with ¹H NMR and ESI-MS but the ¹H NMR values with protons were not specified. Xie *et al.*'s described ¹H NMR values did not correspond with the literature³² and the obtained values in our study.

5,7-Dibromo-8-methoxyquinoline (**3b**) was not observed by the direct bromination of **2b** with 2 equivalents of Br₂; however, we obtained a mixture of **3b** and **3f** in a ratio of 50:50 by using excess amount of molecular bromine. Also **3b** was synthesized by reacting **3a** with dimethylsulphate (Figure 3) in high yield (95%). Before this study, in the literature³²⁻³³ 5,7-dibromo-8-methoxyquinoline **3b** was also synthesized by methyl iodide treatment with lower yields. Treatment of **2b** with Br₂ is the first study to determine regioselectivity in the bromination of 8-OMe **2b**. The information gathered from spectroscopic analysis (NMR and IR) were matched with those in the literature,³² which unambiguously confirmed the structure of **3b**.

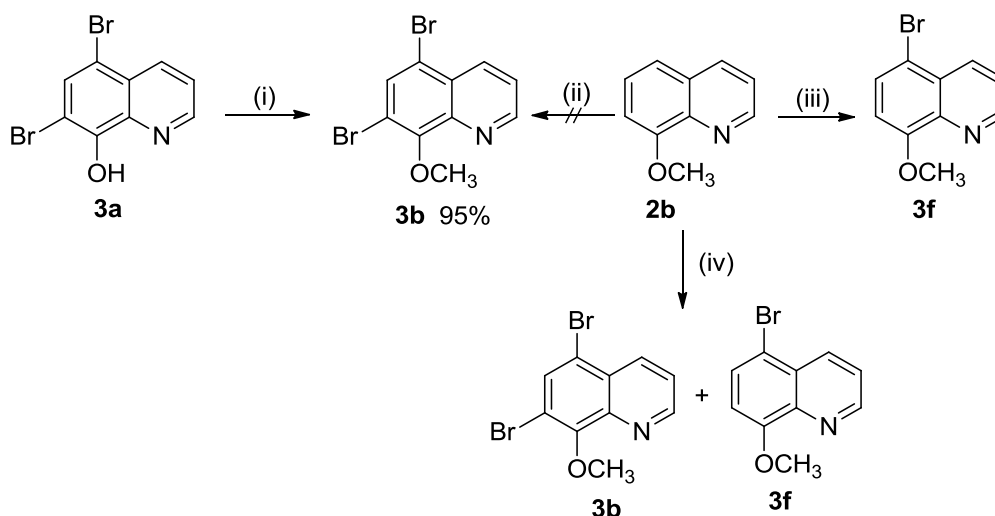


Figure 3. Reagents and conditions. (i) (a) NaOH (1 eq) in distilled H₂O, -10 °C; (b) (CH₃)₂SO₄ (1 eq), -10 °C, 1 h then 70-80 °C, 1 h; (ii) Br₂ (2 eq), CH₂Cl₂, 2 d, rt; (iii) Br₂ (1 eq), CH₂Cl₂, 2 d, rt; (iv) Br₂ (excess), CH₂Cl₂, 2 d, rt.

Table 1. Reaction conditions for synthesis of **3a-f**.

Entry	Substrate	Equivalents of Br ₂	Solvent	Temp. (°C)	Reaction period* (days)	Conversion	Product (ratio) (¹ H NMR)
1	2a	Br ₂ (1.1 eq)	CH ₃ CN	0	1	76%	3a, 3d (34:42)
2	2a	Br ₂ (2.1 eq)	CH ₃ CN	0	1	100%	3a (100)
3	2a	Br ₂ (1.5 eq)	CH ₃ CN	0	1	100%	3a, 3d (42:58)
4	2a	Br ₂ (1.1 eq)	CH ₂ Cl ₂	rt	1	90%	3a, 3d (50:40)
5	2a	Br ₂ (2.1 eq)	CHCl ₃	rt	4	100%	3a (100)
6	2b	Br ₂ (1.1 eq)	CH ₂ Cl ₂	rt	2	100%	3f (100)
7	2b	Br ₂ (2.1 eq)	CH ₂ Cl ₂	rt	2	100%	3f (100)
8	2b	Br ₂ (excess)	CHCl ₃	rt	2	100%	3b (50), 3f (50)
9	2c	Br ₂ (1.5 eq)	CH ₂ Cl ₂	rt	1	100%	3c, 3e (42:58)
10	2c	Br ₂ (2.1 eq)	CH ₂ Cl ₂	rt	1	100%	3c (100)

*All reactions were carried out under dark

To compare how to change bromination selectivity, the phthalonitrile derivatives, **6** and **8**, of 8-OHQ **2a** were also prepared by base-catalysed condensation with 4-nitrophthalonitrile and 4,5-dichlorophthalonitrile. The bromination of **6** and **8** was carried out with 1 and 2 equivalents of bromine. In contrast to **2a**, bromination occurred at C-5 as the bulky phthalonitrile group possibly could hinder the approach of bromine at C-7 (Figure 4).

Though compound **6** was reported³⁴ before, the ¹H NMR and ¹³C NMR values of **6** were not reported in detail. We characterized the structures of **6-9** using detailed ¹H NMR, ¹³C NMR, IR spectra, and elemental analysis.

The preparation of novel phthalonitrile derivatives **6-9** were revealed by the appearance of the absorbance signal of the $\text{C}\equiv\text{N}$ stretching frequency at $\pm 2230\text{cm}^{-1}$ in the IR spectrum. The ¹H NMR splitting pattern of the quinoline fragments of phthalonitrile derivatives **6-9** is almost the same as that of the parent hydroxyquinoline **2a**; however, the appearance of two additional singlets in compound **6** and two doublets and one singlet in compound **8** confirm the attachment of the phthalonitrile moiety. Moreover, the disappearance of the triplet at δ_{H} 7.53 and 7.63 ppm in compounds **6** and **8** indicated the attachment of bromine at position C-5 (Table 2).

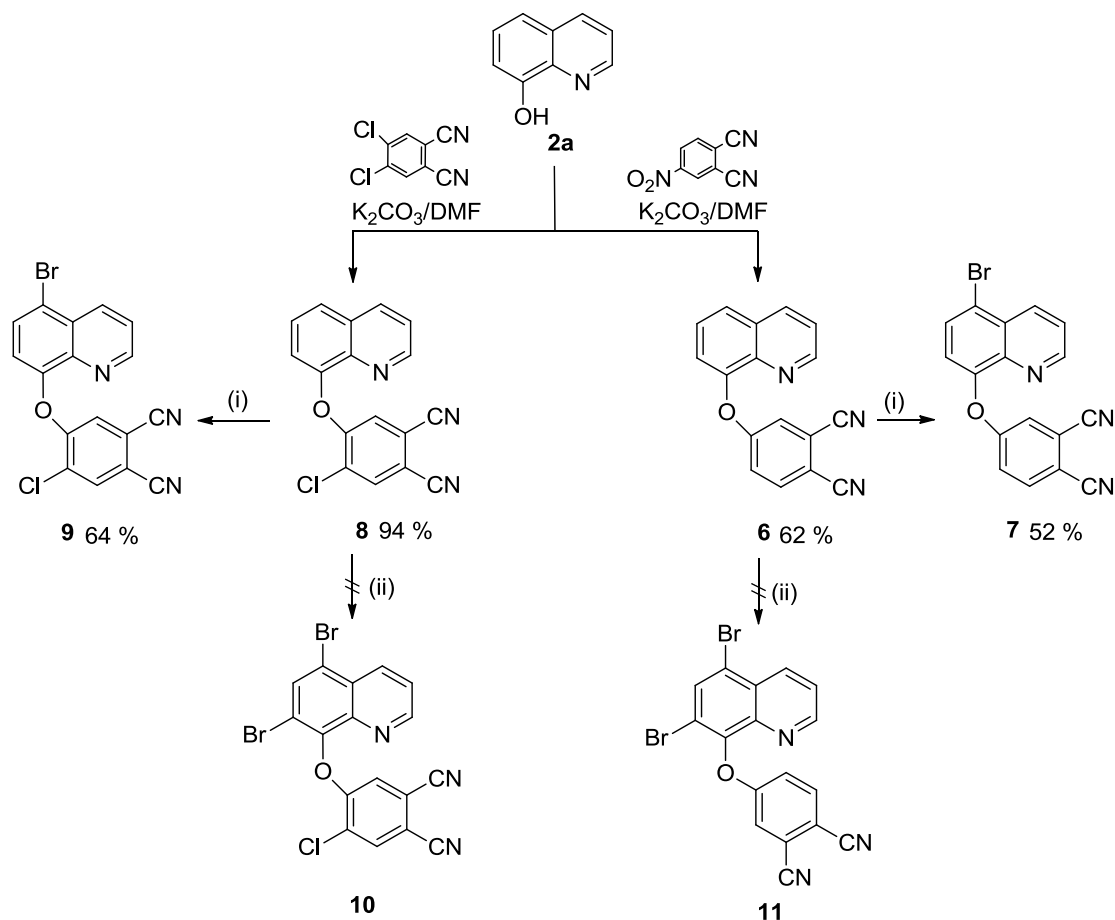


Figure 4. Synthesis and bromination of novel phthalonitrile derivatives (**6** and **8**) Reagents and conditions. (i) Br_2 (1 eq), CH_3CN , $0^\circ C$, 34 h; (ii) Br_2 (2 eq), CH_3CN , $0^\circ C$, 34 h.

Table 2. The selected δ (ppm) with J (Hz) values exhibited by **6-9**

Molecule	H-5	H-7	H-3'	H-5'
6	7.85 (dd, 8.2)	7.50–7.53 (m)	7.19 (d, 2.6)	7.27 (dd, 2.6, 8.8)
7	-	7.71 (d, 8.2)	7.64 (d, 2.6)	7.45 (dd, 2.6, 8.8)
8	7.88 (dd, 8.1)	7.55-7.51(m)	7.92 (s)	-
9	-	7.43 (d, 8.0)	7.92 (t)	-

In conclusion, our study presents the whole aspect of bromination of the 8-substituted quinolines **2a-c** and the phthalonitrile derivatives **6** and **8**. Compounds **2b**, **6** and **8** undergo monobromination (Schemes 3 and 4), while **2a** and **2c** furnished the mixture of mono and dibromo products **3a** and **3c-e** (Schemes 1 and 2). We developed a facile and convenient way based on their solubilities to separate **3a** and **3d** from the mixture (Scheme 1), while the mixture of **3c** and **3e** remained unseparated due to their close R_f values. A new approach was presented to synthesize brominated phthalonitrile derivatives of 8-OHQ **2a** (Scheme 4) in this work. The novel phthalonitrile derivatives (**6**, **8**) were synthesized and brominated with 1 and 2 equivalents of bromine. In both cases, regioselective monobromination occurred at C-5 to afford **7** and **9**, indicating that both phthalonitrile groups weaken the quinoline cycle electronically and sterically

inhibited bromination at C-7 (Scheme 1 and Scheme 4). Our attempt at treating the prepared novel phthalonitrile derivatives with molecular bromine is the first in the literature.

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