DOI 10.1515/hc-2013-0088 — Heterocycl. Commun. 2013; 19(6): 405–409

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Synthesis of 2-[(quinolin-8-yloxy)methyl]-quinoline-3-carboxylic acid derivatives

Abstract: A simple and concise one-pot protocol for the synthesis of carboxyl-substituted bisquinoline systems **3a–i** is described. The approach involves the Williamson reaction of ethyl 2-(halomethyl)quinoline-3-carboxylates **4a–c** with 8-hydroxyquinolines **5a–c** followed by hydrolysis.

Keywords: bisquinoline; carboxylic acid; ester hydrolysis; one-pot; Williamson reaction; 8-hydroxyquinoline.

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Introduction

Bisquinolines display potent antimalarial activity [1–4]. Some well-known bisquinoline drugs such as piperaquine, hydroxypiperaquine [5–7], WR 268,668 B [8], and *N,N′*-bis (-7-chloroquinolin-4-yl) alkanediamine [9] are active against chloroquine resistant strains of malaria. Some new bisquinoline derivatives also possess interesting *in vitro* antileishmanial [10], antitumor [11], antiprotozoal and antimicrobial activities [12] by forming a complex with the DNA double helix. Palit et al. [10] has reported that 1,1-bis-[(5-chloro-8-quinolyl) oxy]methane (**1**, Figure 1) exhibits the most significant antileishmanial activity. Besides, these structures have also been invoked as functional molecules within the domain of coordination chemistry and supramolecular chemistry [13–15]. Consequently, wide demands in various fields have stimulated the development of efficient methods for the synthesis of bisquinoline derivatives, including Knoevenagel condensation reaction of quinaldine with aromatic dialdehydes [16], double Friedlander reaction of 2-aminobenzophenone with substituted diphenacylsulfides [17] or arylacetyl(4-acetylphenyl) ethers [18], PTC mediated alkylation reaction of 8-hydroxyquinolines with dibromoxylenes, dibromonaphthalenes, and dibromoquinoxalenes [19], and other routes [20, 21]. In this regard, Zhao et al. [22] have reported a new access to a unique ether **2** (Figure 1).

This work is concerned with the synthesis of carboxylic acid derivatives of the general structure **3**. Quinolinecarboxylic acids are important substructures in a number of molecules which exhibit potent antimycobacterial [23] and antiviral [24] properties, and could be used as inhibitors of the IGF/IGFBP-3 complex [25] or cyclooxygenase-2 inhibitors [26]. In addition, quinolinecarboxylic acids are important synthetic intermediates or building blocks for synthesis of valuable quinoline drugs [27]. Therefore, not surprisingly, the quinolinecarboxylic acid framework has been an attractive synthetic target, and numerous efforts have been invested in exploring new structures of such compounds [28–31].

Results and discussion

The synthetic route to the desired bisquinolinecarboxylic acids **3a–i**, by the one-pot reaction between ethyl 2-(halomethyl)quinoline-3-carboxylates **4a–c** and 8-hydroxyquinolines **5a–c** is summarized in Scheme 1.

Ethyl 2-(chloro/bromomethyl)quinoline-3-carboxylate derivatives are viewed as ideal starting materials for the flexible synthesis of a large range of quinoline derivatives because of the presence of the active chloro/bromomethyl group [32–34]. However, we have not yet found any literature reported on their reaction with 8-hydroxylquinolines for construction of the bisquinoline skeleton. Thus, on the basis of our previous work [35–38], 2-chloromethylquinoline (**4c**) was first subjected to the Williamson reaction with 8-hydroxylquinoline (**5a**) in the presence of K_2CO_3 in MeCN. It was found that the reaction proceeded well and the thin layer chromatography (TLC) analysis did not indicate the formation of any distinct byproduct. The Williamson reaction in the presence of K_2CO_3 can also be run in other solvents such as *N,N*-dimethylformamide (DMF) to give comparable yields. MeCN remained the solvent of choice only because of its low boiling point, which would bring much convenience in the workup procedure. However, when using KOH, $NaHCO_3$ or NaOAc as base under the same reaction conditions, the corresponding bisquinolines **3** were obtained in much lower yields. Upon the completion of the Williamson reaction as observed by

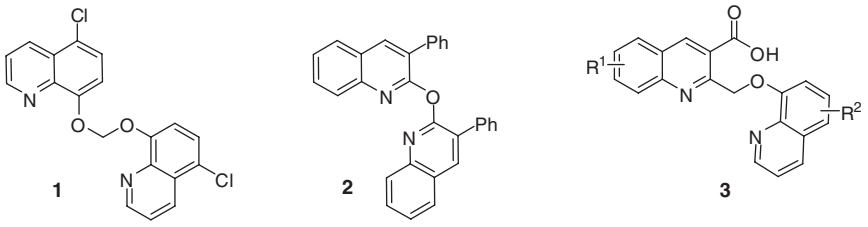
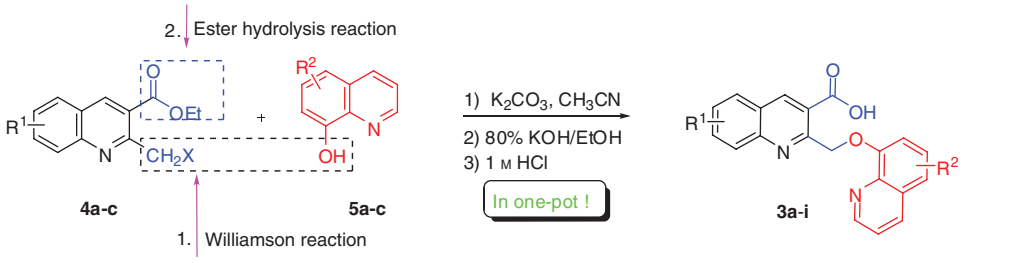


Figure 1 Structures of bis-quinoline compounds **1–3**.



4a: R^1 = H; X = Br
4b: R^1 = [1,3]dioxolo[4,5-*g*]; X = Br
4c: R^1 = benzo[*h*]; X = Cl
5a: R^2 = H
5b: R^2 = 5,7-$(Cl)_2$
5c: R^2 = 5,7-$(Br)_2$
3a: R^1 = H; R^2 = H
3b: R^1 = H; R^2 = 5,7-$(Cl)_2$
3c: R^1 = H; R^2 = 5,7-$(Br)_2$
3d: R^1 = [1,3]dioxolo[4,5-*g*]; R^2 = H
3e: R^1 = [1,3]dioxolo[4,5-*g*]; R^2 = 5,7-$(Cl)_2$
3f: R^1 = [1,3]dioxolo[4,5-*g*]; R^2 = 5,7-$(Br)_2$
3g: R^1 = benzo[*h*]; R^2 = H
3h: R^1 = benzo[*h*]; R^2 = 5,7-$(Cl)_2$
3i: R^1 = benzo[*h*]; R^2 = 5,7-$(Br)_2$

Scheme 1

TLC, MeCN was simply evaporated, 80% ethanolic potassium hydroxide solution was directly added to the residue, and the resulting mixture was stirred under reflux. When the alkaline hydrolysis reaction was complete (usually within 2 h) followed by acidifying the solution with 1 M HCl, the desired carboxyl-substituted bisquinoline compounds were obtained in high yields (82–95%) after recrystallization from ethanol. The structures of compounds **3a–i** were confirmed by spectroscopic analysis. The advantage of this method is that two chemical transformations, that is, Williamson ether synthesis and subsequent ester hydrolysis, take place in one-pot, thereby providing the products in high yields with operational and experimental simplicity.

Conclusions

A facile one-pot synthesis of 2-[(quinolin-8-yloxy)methyl]-quinoline-3-carboxylic acid derivatives is described. Readily available starting materials, mild reaction conditions, short reaction times, satisfactory yields and the use of a non-toxic and inexpensive base contribute to the usefulness of this method.

Experimental

All reagents were obtained from Fluka and used without purification. Melting points (uncorrected) were determined by using WRS-1B melting points apparatus. ^{1}H NMR (600 MHz) and ^{13}C NMR (150 MHz) spectra were recorded on a Brucker AVANCE NMR spectrometer. HRMS (ESI) data were acquired on a Bruker Customer micrOTOF-Q 125 high-resolution mass spectrometer. The progress of reactions was monitored by TLC on silica gel GF254 using ethyl acetate/petroleum ether (1:6) as eluent. Analytical grade MeCN was used for the chemical synthesis.

General procedure for the one-pot synthesis of 2-[(quinolin-8-yloxy)methyl]quinoline-3-carboxylic acid derivatives 3a–i

A mixture of ethyl 2-(halomethyl)quinoline-3-carboxylate (**4a–c**, 1 mmol), 8-hydroxyquinoline (**5a–c,** 1.1 mmol) and anhydrous K_2CO_3 (3 mmol, 0.48 g) was stirred in refluxing MeCN (10 mL) for 3 h. After the reaction was complete, MeCN was evaporated to dryness. Then a solution of KOH (1.12 g, 20 mmol) in 80% ethanol (25 mL) was added directly to the residue and the mixture was heated under reflux for an additional 2 h. After completion, the reaction mixture was cooled, acidified to pH 4–5 with 1 mol/L HCl. The precipitate was collected by filtration and then washed with 25% NH_4OH solution and water. The crude product was crystallized from ethanol to afford compounds **3a–i** in 82–95% yield.

2-[(Quinolin-8-yloxy)methyl]quinoline-3-carboxylic acid (3a) Yellow crystals from **5a**; reaction time 5 h; yield 88%; mp 206–207°C; ^{1}H NMR (DMSO-d_6): δ 5.95 (s, 2H), 7.56 (d, 1H, *J* = 7.5 Hz), 7.66 (t, 1H, *J* = 8 Hz), 7.72 (m, 2H), 7.83 (dd, 1H, *J* = 8, 7.5 Hz), 7.88 (m, 1H), 7.93 (d, 1H, *J* = 8 Hz), 8.20 (d, 1H, *J* = 8 Hz), 8.76 (d, 1H, *J* = 8 Hz), 8.98 (d, 1H, *J* = 3.6 Hz), 9.00 (s, 1H), 13.41 (s, br, 1H); ^{13}C NMR ($CDCl_3$): δ 76.2, 115.2, 115.5, 123.4, 125.0, 125.6, 125.9, 126.0, 127.5, 130.6, 133.1, 135.7, 142.0, 142.5, 145.7, 149.4, 150.8, 152.3, 159.4, 166.6. HRMS (ESI): Calcd for $C_{20}H_{14}N_2NaO_3^+$: m/z 353.0895, found m/z 353.0902.

2-[(5,7-Dichloroquinolin-8-yloxy)methyl]quinoline-3-carboxylic acid (3b) Yellow solid from **5b**; reaction time 5 h; yield 95%; mp 189–191°C; ^{1}H NMR (DMSO-d_6) δ: 6.19 (s, 2H), 7.69 (t, 1H, *J* = 8 Hz), 7.75 (d, 1H, *J* = 8 Hz), 7.83 (s, 1H), 7.88 (m, 1H), 7.95 (d, 1H, *J* = 8 Hz), 8.17 (d, 1H, *J* = 8 Hz), 8.56 (d, 1H, *J* = 8 Hz), 8.96 (s, 1H), 9.03 (d, 1H, *J* = 3.6 Hz), 13.39 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 76.6, 123.0, 124.3, 124.7, 125.3, 125.7, 126.4, 127.5, 127.7, 128.6, 129.0, 132.0, 133.1, 140.1, 142.7, 147.5, 150.6, 151.0, 155.6, 167.2. ESI-MS m/z: 398.9 (100%, M+H)$^+$; HRMS (ESI): Calcd for $C_{20}H_{12}{}^{35}Cl_2N_2NaO_3^+$: m/z 421.0115, found m/z 421.0106.

2-[(5,7-Dibromoquinolin-8-yloxy)methyl]quinoline-3-carboxylic acid (3c) White solid from **5c**; reaction time 5 h; yield 92%; mp 181–182°C; ^{1}H NMR (DMSO-d_6): δ 5.83 (s, 2H), 7.13 (t, 1H, *J* = 8 Hz), 7.48 (d, 1H, *J* = 8 Hz), 7.62 (s, 1H), 7.71 (d, 1H, *J* = 8 Hz), 7.89 (m, 2H), 7.99 (d, 1H, *J* = 8 Hz), 8.18 (d, 1H, *J* = 4 Hz), 8.98 (s, 1H), 13.45 (s, br, 1H); ^{13}C NMR ($CDCl_3$): δ 76.2, 123.0, 124.8, 125.0, 125.3, 125.6, 125.7, 126.0, 127.5, 128.3, 130.5, 133.1, 142.0, 142.5, 145.7, 149.3, 150.3, 151.0, 159.4, 166.6. HRMS (ESI): Calcd for $C_{20}H_{12}{}^{79}Br_2N_2NaO_3^+$: m/z 508.9105, found m/z 508.9098.

6-[(Quinolin-8-yloxy)methyl]-[1,3]dioxolo[4,5-*g*]quinoline-7-carboxylic acid (3d) White crystals from **5a**; reaction time 5 h; yield 86%; mp 248–249°C; ^{1}H NMR (DMSO-d_6): δ 5.72 (s, 2H), 6.28 (s, 2H), 7.34 (s, 1H), 7.41 (s, 1H), 7.57 (d, 1H, *J* = 4 Hz), 7.66 (m, 2H), 8.20 (m, 2H), 8.31 (d, 1H, *J* = 8 Hz), 8.91 (s, 1H), 13.17 (s, br, 1H); ^{13}C NMR (DMSO-d_6): δ 71.3, 102.7, 103.5, 104.8, 109.9, 119.8, 121.9, 122.9, 123.9, 126.9, 129.1, 135.9, 138.6, 139.8, 146.5, 148.6, 148.9, 152.6, 153.0, 154.7, 168.3. HRMS (ESI): Calcd for $C_{21}H_{14}N_2NaO_5^+$: m/z 397.0793, found m/z 397.0789.

6-[(5,7-Dichloroquinolin-8-yloxy)methyl]-[1,3]dioxolo[4,5-*g*]-quinoline-7-carboxylic acid (3e) White solid from **5b**; reaction time 5 h; yield 82%; mp 198–200°C; ^{1}H NMR (DMSO-d_6): δ 6.11 (s, 2H), 6.26 (s, 2H), 7.28 (s, 1H), 7.51 (s, 1H), 7.74 (s, 1H), 7.86 (dd, 1H, *J* = 8 Hz, 4 Hz), 8.55 (d, 1H, *J* = 8 Hz), 8.73 (d, 1H, *J* = 4 Hz), 9.04 (s, 1H), 13.18 (s, br, 1H); ^{13}C NMR (DMSO-d_6): δ 76.6, 102.6, 103.4, 104.8, 122.3, 123.0, 123.6, 124.6, 125.3, 125.7, 127.4, 133.1, 138.5, 142.7, 146.4, 148.4, 150.7, 151.0, 152.5, 153.4, 168.3. HRMS (ESI): Calcd for $C_{21}H_{12}{}^{35}Cl_2N_2NaO_5^+$: m/z 465.0013, found m/z 465.0019.

6-[(5,7-Dibromoquinolin-8-yloxy)methyl]-[1,3]dioxolo[4,5-*g*]-quinoline-7-carboxylic acid (3f) Yellow solid from **5c**; reaction time 5 h; yield 85%; mp 202–204°C; ^{1}H NMR (DMSO-d_6): δ 6.14 (s, 2H), 6.26 (s, 2H), 7.30 (s, 1H), 7.51 (s, 1H), 7.79 (s, 1H), 8.10 (dd, 1H, *J* = 8 Hz, 4.2 Hz), 8.48 (d, 1H, *J* = 8 Hz), 8.74 (d, 1H, *J* = 4 Hz), 9.00 (s, 1H), 13.17 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 76.0, 103.0, 105.7, 111.1, 113.5, 115.6, 119.3, 121.9, 123.7, 127.9, 134.4, 141.6, 144.3, 146.6, 149.6, 151.2, 152.3, 153.4, 153.8, 155.7, 168.3. HRMS (ESI): Calcd for $C_{21}H_{12}{}^{79}Br_2N_2NaO_5^+$: m/z 552.9003, found m/z 552.9007.

2-[(Quinolin-8-yloxy)methyl]benzo[*h*]quinoline-3-carboxylic acid (3g) White solid from **5a**; reaction time 5 h; yield 83%; mp 227–229°C; ^{1}H NMR (DMSO-d_6): δ 5.80 (s, 2H), 7.41 (d, 1H, *J* = 8 Hz), 7.50 (m, 2H), 7.57 (m, 1H), 7.74 (t, 1H, *J* = 8 Hz), 7.88 (t, 1H, *J* = 8 Hz), 8.06 (m, 3H), 8.10 (d, 1H, *J* = 8 Hz), 8.14 (d, 1H, *J* = 4 Hz), 8.20 (d, 1H, *J* = 8 Hz), 8.95 (s, 1H), 13.45 (s, br, 1H); ^{13}C NMR (DMSO-d_6): δ 71.0, 110.1, 119.8, 121.8, 124.3, 124.9, 125.3, 125.6, 126.9, 127.4, 128.2, 128.6, 129.2, 129.3, 130.1, 134.2, 135.9, 139.6, 139.9, 145.8, 149.0, 154.5, 154.8, 167.2. HRMS (ESI): Calcd for $C_{24}H_{16}N_2NaO_3^+$: m/z 403.1051, found m/z 403.1046.

2-[(5,7-Dichloroquinolin-8-yloxy)methyl]benzo[*h*]quinoline-3-carboxylic acid (3h) White solid from **5b**; reaction time 5 h; yield 90%; mp 233–235°C; ^{1}H NMR (DMSO-d_6): δ 6.49 (s, 2H), 7.62 (t, 1H, *J* = 8 Hz), 7.72 (m, 3H), 7.87 (s, 1H), 7.96 (dd, 1H, *J* = 8 Hz, 7.5 Hz), 8.01 (d, 1H, *J* = 8 Hz), 8.49 (d, 1H, *J* = 8 Hz), 8.57 (d, 1H, *J* = 8 Hz), 8.88 (d, 1H, *J* = 4 Hz), 9.03 (s, 1H), 13.49 (s, br, 1H); ^{13}C NMR (DMSO-d_6): δ 75.6, 122.9, 124.1, 124.6, 125.1, 125.6, 125.7, 127.0, 127.5, 128.1, 128.2, 128.7, 129.1, 130.1, 131.6, 131.8, 133.1, 134.0, 139.1, 142.8, 145.4, 150.7, 154.8, 167.0. HRMS (ESI): Calcd for $C_{24}H_{14}{}^{35}Cl_2N_2NaO_3^+$: m/z 471.0272, found m/z 471.0274.

2-[(5,7-Dibromoquinolin-8-yloxy)methyl]benzo[*h*]quinoline-3-carboxylic acid (3i) Yellow solid from **5c**; reaction time 5 h; yield 87%; mp 213–215°C; ^{1}H NMR (DMSO-d_6): δ 6.46 (s, 2H), 7.42 (dd, 1H, *J* = 8 Hz, 7 Hz), 7.70 (m, 2H), 7.78 (d, 1H, *J* = 8 Hz), 7.99 (s, 1H), 8.03 (d, 1H, *J* = 8 Hz), 8.10 (s, 1H), 8.50 (d, 1H, *J* = 8 Hz), 8.54 (d, 1H, *J* = 8 Hz), 8.96 (d, 1H, *J* = 4 Hz), 9.02 (s, 1H), 13.52 (s, br, 1H); ^{13}C NMR (DMSO-d_6): δ 76.0, 114.5, 115.7, 116.1, 123.5, 125.6, 126.2, 127.5, 127.7, 127.9, 128.4, 128.6, 129.3, 130.6, 133.2, 135.4, 135.8, 142.7, 145.7, 146.6, 151.0, 151.9, 152.3, 168.3. HRMS (ESI): Calcd for $C_{24}H_{14}{}^{79}Br_2N_2NaO_3^+$: m/z 558.9261, found m/z 558.9265.

Acknowledgments: The authors would like to thank the Scientific Research Foundation of the Education Department of Liaoning Province (Grant No. L2013428) for financial support.

Received June 3, 2013; accepted October 13, 2013

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