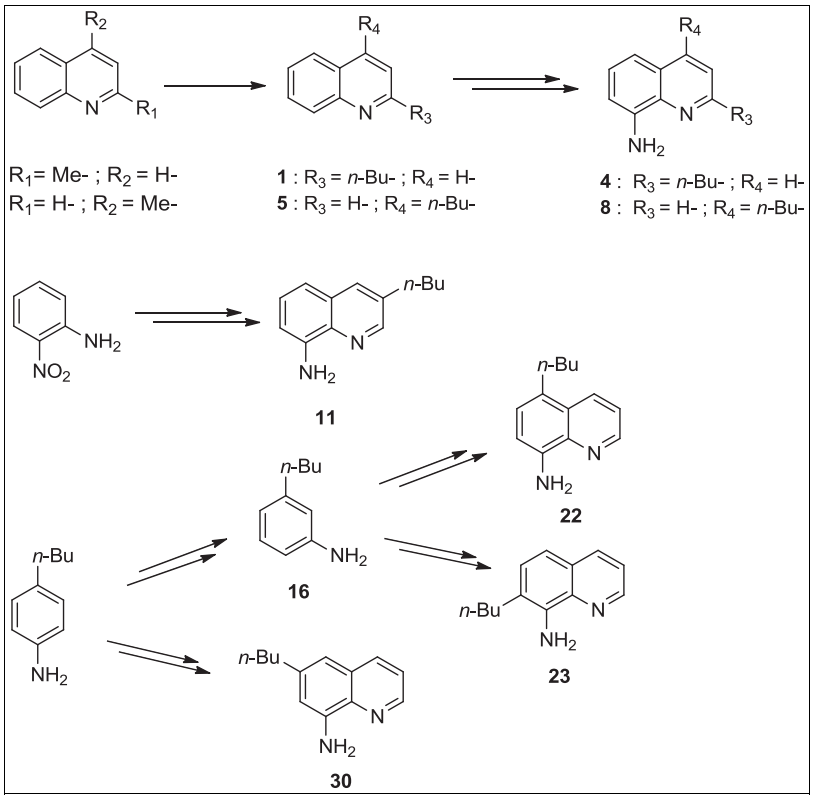
A Systematic Study on the Synthesis of *n*-Butyl Substituted 8-Aminoquinolines

Ahmet Koseoglu,[a] Turan Gul,[b] and Ali Ersin Acar[a]*

[a]Department of Chemistry, Bogazici University, Bebek, Istanbul, 34342, Turkey
[b]Analytical Biochemistry, Department of Pharmacy, University of Groningen, Groningen, The Netherlands
*E-mail: ersin.acar@boun.edu.tr

Received October 14, 2014
DOI 10.1002/jhet.2399
Published online 26 March 2015 in Wiley Online Library (wileyonlinelibrary.com).



A systematic study on the synthesis of 8-aminoquinoline derivatives with an *n*-butyl group at each alternate position of the quinoline ring was carried out. Skraup Reaction and its Doebner–von Miller variation were used to obtain most of the quinoline ring except for the 2-butyl-8-aminoquinolines and 4-butyl-8-aminoquinolines where the commercially available methylquinoline derivatives were used as precursors. The structures of the synthesized compounds were characterized by FTIR, ^{1}H-NMR, COSY, ^{13}C-NMR and HRMS spectra.

J. Heterocyclic Chem., **53**, 263 (2016).

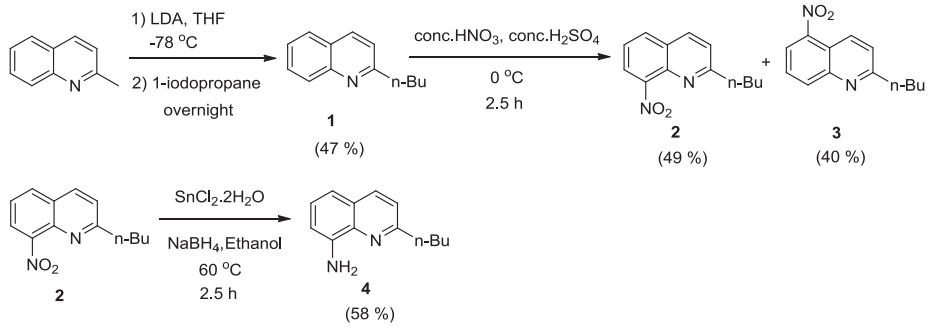
INTRODUCTION

Quinolines are key intermediates to important groups of compounds such as drugs [1–6], dyes [7], polymers [8–10] and fluorophores [11,12]. They have found uses in medicine such as antimalarial [13] and anticancer drugs [14]. The amino-substituted quinolines are found both in natural products and synthetically prepared drugs. The 8-aminoquinoline primaquine [5] and the 4-aminoquinoline chloroquine [6] are examples to such aminoquinoline drugs. Owing to this wide area of application, synthesis of aminoquinolines is especially of great importance.

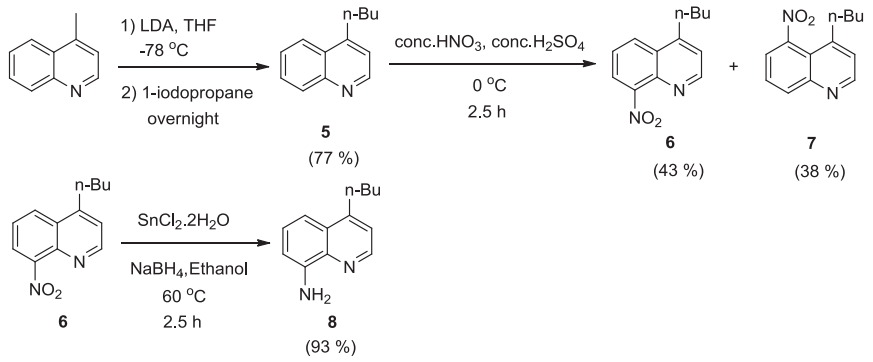
Substituted quinolines can provide the diversity necessary to build libraries of compounds whose members can exhibit different biological effects. Compared with their naphthalene bioisosteres, which are similar in size, quinolines can bear on many different R groups on different positions thanks to the diverse chemistries that can be used. The substitution on the quinoline ring can be introduced in the pre-cyclization or post-cyclization steps [15–21]. This aspect of the quinoline chemistry makes it possible to explore structure-activity relationships (SAR) broadly and construct bigger libraries of compounds in the drug researches. In such an effort, we became interested in the synthesis of 8-aminoquinolines with a butyl substituent where the position of the butyl group was subject to change.

Many examples can be found in literature on the syntheses of substituted quinolines [19–25], but there has been no

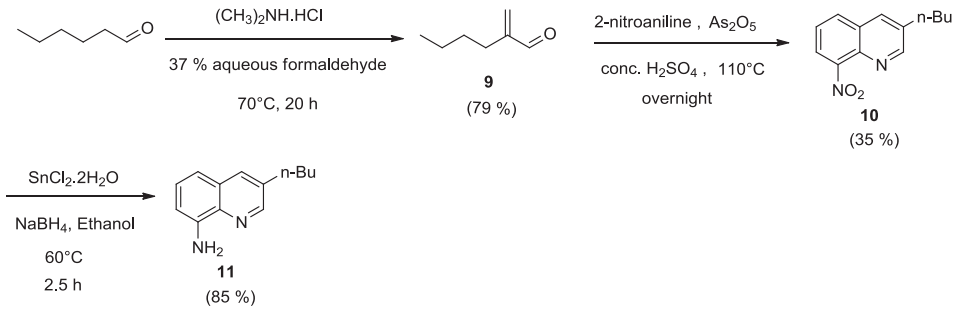
Scheme 1. Synthesis of 8-amino-2-butylquinoline **4**.



Scheme 2. Synthesis of 8-amino-4-butylquinoline **8**.



Scheme 3. Synthesis of 8-amino-3-butylquinoline **11**.



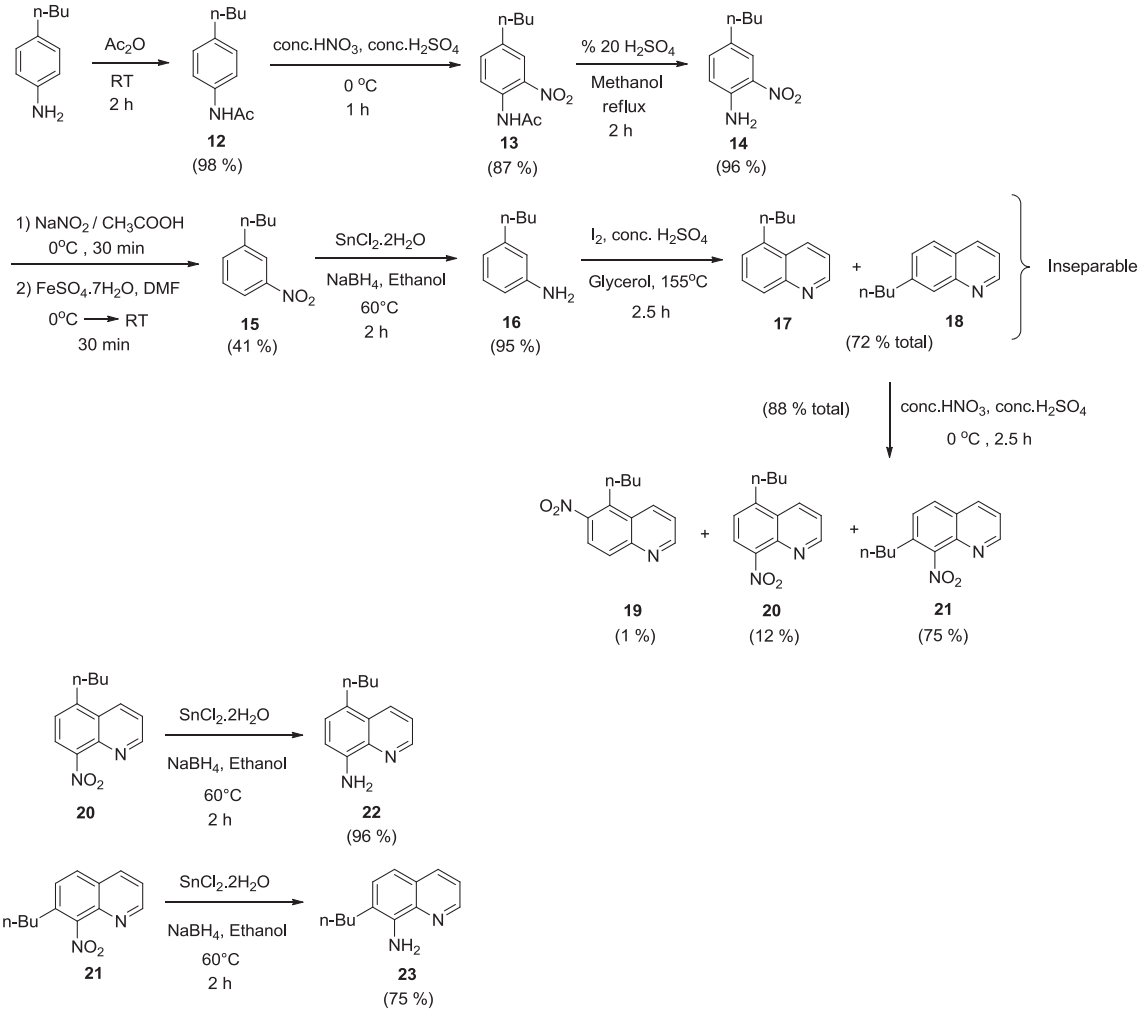
systematic study on the syntheses of (monoalkyl)-8-aminoquinolines substituted at each alternate position of the quinoline ring. In this manuscript, a systematic study on the synthesis of 8-aminoquinoline derivatives with an *n*-butyl group at each alternate position of the quinoline ring is presented.

RESULTS AND DISCUSSION

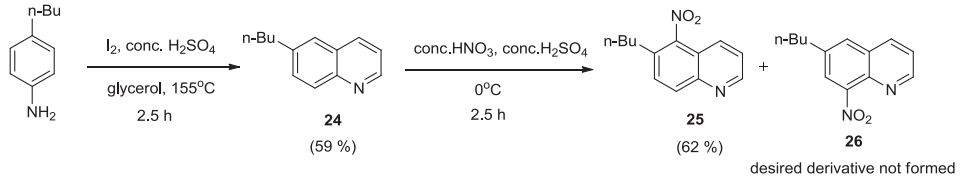
As a general approach, Skraup Reaction and its Doebner–von Miller variation were used to obtain the quinoline ring except for the 2-butyl-8-aminoquinolines and 4-butyl-8-aminoquinolines, where the commercially available methyl quinoline derivatives were used as precursors.

Syntheses of 8-amino-2-butylquinoline (4) and 8-amino-4-butylquinoline (8). Compounds **4** and **8** were synthesized starting from 2-methylquinoline and 4-methylquinoline, respectively (Schemes 1 and 2). When the methyl group is on the positions 2- and 4- on the quinoline ring, its protons are acidic enough to be abstracted by a strong base, and the resulting carbanion is prone to electrophilic attack. Thus, syntheses of 2-butylquinoline **1** and 4-butylquinoline **5** were accomplished by the chain extension of 2-methylquinoline (quinaldine) and 4-methylquinoline (lepidine), respectively, using LDA and 1-iodopropane. Nitration of **2** and **7** each gave both 8-nitro and 5-nitro isomers. After the separation of the isomers, the subsequent reduction of 2-butyl-8-nitroquinoline **2** and 4-butyl-8-nitroquinoline **6** by $SnCl_2.2H_2O/NaBH_4$ gave **4** and **8**.

Scheme 4. Synthesis of 8-amino-5-butylquinoline **22** and 8-amino-7-butylquinoline **23**.



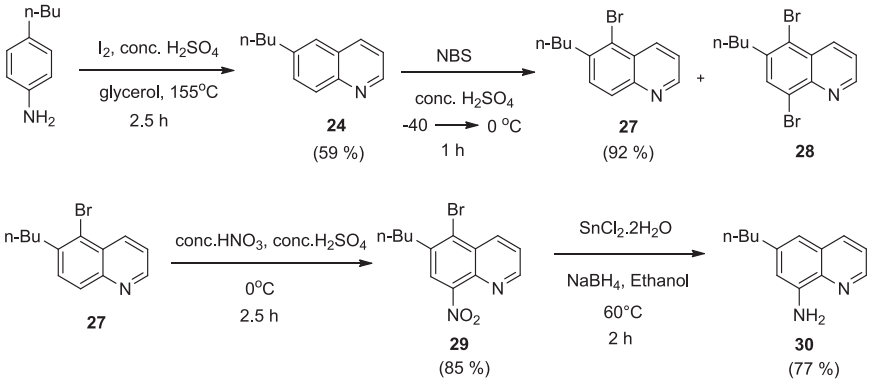
Scheme 5. The tentative synthetic route to 6-butyl-8-nitroquinoline **26**



Synthesis of 8-amino-3-butylquinoline (11). Compound **11** was synthesized starting from 2-methylenehexanal and 2-nitroaniline by Doebner–von Miller variation of Skraup Reaction (Scheme 3). Both of the quinoline substituents, the nitro group and the butyl group, were simultaneously introduced during the ring formation. Hexanal was treated with 37% aqueous formaldehyde and dimethylamine hydrochloride to give 2-methylenehexanal **9**. The next step involved the cyclization of **9** and 2-nitroaniline to obtain the 3-butyl-8-nitroquinoline **10**, which was then reduced by $SnCl_2/NaBH_4$ to give the desired product **11**.

Syntheses of 8-amino-5-butylquinoline (22) and 8-amino-7-butylquinoline (23). The syntheses of **22** and **23** started by the cyclization of butyl anilines to corresponding butyl quinolines using the Skraup reaction, where the position of the butyl group on the aniline ring dictated its final position on the 8-aminoquinoline (Scheme 4). The route to 8-amino-5-butylquinoline **22** and 8-amino-7-butylquinoline **23** begins with the multi-step synthesis of 3-butylaniline **16** from the commercially available 4-butylaniline. 4-Butylaniline was first protected by acetylation. After the standard nitration and the

Scheme 6. The successful synthetic route to 8-amino-6-butylquinoline **30**.



deprotection steps, the amino group of the 4-butyl-2-nitroaniline **14** was removed by forming the corresponding diazonium salt followed by *in situ* deazotization to give 1-butyl-3-nitrobenzene **15**. The reduction of **15** gave **16,** which was then cyclized with glycerol using the Skraup reaction to give 7-butylquinoline **18** and 5-butylquinoline **17**. The crude products were subjected to column chromatography, but the products were inseparable. In order to elucidate the structures of **17** and **18**, a small portion of the mixture was separated by thin layer chromatography on silica plates. However, the next reaction was continued with the nitration step where the mixture of the two isomers **17** and **18** was used directly. The nitration reaction gave a mixture of 5-butyl-6-nitroquinoline **19**, 5-butyl-8-nitroquinoline **20** and 7-butyl-8-nitroquinoline **21,** which were successfully separated by column chromatography using silica and hexane/dichloromethane (3/1) mixture as the eluent. The subsequent reductions of **20** and **21** gave 8-amino-5-butylquinoline **22** and 8-amino-7-butylquinoline **23,** respectively.

Synthesis of 8-amino-6-butylquinoline (30). The synthesis of **30** was initially designed as shown in Scheme 5 where the 6-butylquinoline **24** was synthesized by Skraup method starting from 4-butylaniline. However, the nitration of 6-butylquinoline **24** did not give the desired 8-nitro isomer **30**. Instead, it led to the exclusive formation of 6-butyl-5-nitroquinoline **25**. Therefore, a different strategy was used to produce 8-amino-6-butylquinoline **30** (Scheme 6) [25]. Because the 5th position of **24** is the most reactive for the nucleophilic aromatic substitution reaction, it was first blocked by bromination with *N*-bromosuccinimide to give a mixture of 5-bromo-6-butylquinoline **27** and 5,8-dibromo-6-butylquinoline **28**. After the necessary separation, the nitration of **27** gave 5-bromo-6-butyl-8-nitroquinoline **29** as the only product. The standard reduction procedure with $SnCl_2.2H_2O/NaBH_4$ to reduce the nitro group to the amino group resulted in simultaneous removal of the bromine substituent to give the final product **30**.

CONCLUSION

In summary, we presented the syntheses of 8-aminoquinolines with an *n*-butyl group in all possible positions. The methods employed in this work can be used to introduce a variety of alkyl groups to the core aminoquinoline ring. The systematic syntheses of such compounds might be useful in building libraries of compounds with potential biological activity.

EXPERIMENTAL

General. The starting materials and reagents were purchased from Aldrich. Melting points were determined on Stuart SMP11 melting point apparatus (Bibby Scientific Limited, Staffordshire, UK). Fourier Transform Infrared Spectroscopy (FTIR) characterizations were performed on a Thermo Nicolet 380 FT-IR equipped with Smart Orbit diamond ATR accessory. Analytical Chromatography was performed on silica gel 60 F_{254} TLC plates. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on Varian 400 MHz NMR spectrometer (Varian Associates, Palo Alto, CA, USA) using TMS as internal standard. Correlations were established using ^{1}H-^{1}HCOSY experiments. High resolution mass spectra (HRMS) were obtained by using electrospray ionization (ESI) with Micro-Tof; m/z values are reported.

2-butylquinoline (1) [21]. In order to prepare the lithium diisopropylamide (LDA) solution, in a 25-mL flask equipped with a magnetic stirrer, diisopropylamine (1.83 mL, 13.1 mmol) was dissolved in 12 mL dry THF under N_2 at −78°C. To this solution, 2.5 M *n*-buLi in hexane (5.68 mL, 14.2 mmol) was added, and the mixture was warmed to 0°C in 30 min. Then, the mixture was cooled to −78°C. In order to form the carbanion, 40 mL dry THF was put into a 250 mL round-bottom flask with a magnetic stirrer. To this solution, quinaldine (1.49 mL, 11 mmol) was added under N_2 at −78°C. The prepared LDA solution was added to this solution at −78°C. The color of the solution changed to dark orange. This mixture was kept at −78°C for 2.5 h. Iodopropane (1.39 mL, 14.2 mmol) was then added dropwise to this mixture at −78°C under N_2, and this mixture was kept at −78°C for 3 h. The resulting mixture was allowed to warm up to room temperature overnight. The color of the solution turned to light orange. The reaction was then quenched with saturated 20 mL NH_4Cl

and extracted with 3 × 50-mL ethyl acetate. The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The product was further purified by column chromatography using silica gel as the packing material and ethyl acetate as the mobile phase. After evaporation of the solvent, a yellow viscous liquid was obtained, 0.96 g (47%); FTIR (v, cm^{-1}): 3056, 2955, 2928, 1618, 1600, 1503, 1465, 1426, 1310, 1116, 824, 754; ^{1}H-NMR ($CDCl_3$), δ: 0.76 (t, 3H, J = 7.6 Hz), 1.24 (m, 2H), 1.60 (m, 2H), 2.76 (t, 2H, J = 7.6 Hz), 6.94 (d, 1H, J = 8.8 Hz), 7.18 (t, 1H, J = 7.6, 7.2 Hz), 7.40 (d, 1H, J = 8.0 Hz), 7.44 (d, 1H, J = 8.8 Hz), 7.68 (d, 1H, J = 8.4 Hz), 7.92 (d, 1H, J = 8.8 Hz) ppm; ^{13}C-NMR ($CDCl_3$), δ: 13.82, 22.49, 31.88, 38.80, 121.08, 125.36, 126.54, 127.27, 128.72, 129.01, 135.82, 147.82, 162.70 ppm; HRMS (ESI): (m/z) calcd. for $C_{13}H_{16}N$ $[M+H]^+$: 186.1283, found: 186.1257.

2-butyl-8-nitroquinoline (2) [26]. To an ice-bath-cooled solution of 2-butylquinoline **1** (0.556 g, 3 mmol) in 1.25 mL concentrated H_2SO_4, was added drop wise 1 mL of concentrated H_2SO_4/HNO_3 mixture (3:1). Reaction was maintained at 0°C, stirred and monitored by TLC until all the quinoline had been consumed (2.5 h). Mixture was diluted with 10 mL water, and NaOH(s) was added until the pH reached 10–11. Solution was extracted with 3 × 50 mL CH_2Cl_2, dried over anhydrous Na_2SO_4, filtered and evaporated. Nitration of 2-butylquinoline **1** resulted in 2-butyl-8-nitroquinoline **2** and 2-butyl-5-nitroquinoline **3**. In order to separate 2-butyl-8-nitroquinoline **2**, a column was prepared using silica gel and CH_2Cl_2 as the eluent phase. 2-butyl-8-nitroquinoline **2** was concentrated under reduced pressure to afford a yellowish solid, 0.34 g (49%), mp not determined, decomposes upon heating; FTIR (v, cm^{-1}): 2957, 2929, 2871, 1602, 1527, 1499, 1465, 1430, 1357, 1312, 870, 795, 761; ^{1}H-NMR ($CDCl_3$), δ: 0.94 (t, 3H, J = 7.2 Hz), 1.39 (m, 2H), 1.78 (m, 2H), 2.97 (t, 2H, J = 8.0 Hz), 7.39 (d, 1H, J = 8.8 Hz), 7.50 (t, 1H, J = 8.0, 7.6 Hz), 7.91 (dd, 1H, J = 7.2, 1.2 Hz), 7.95 (dd, 1H, J = 8.4, 1.2 Hz), 8.09 (d, 1H, J = 8.8 Hz) ppm; ^{13}C-NMR ($CDCl_3$), δ: 13.87, 22.45, 31.07, 38.83, 123.01, 123.20, 124.13, 127.57, 131.26, 135.66, 139.17, 148.00, 165.84 ppm; HRMS (ESI): (m/z) calcd. for $C_{13}H_{15}N_2O_2$ $[M+H]^+$: 231.1134, found: 231.1124.

8-amino-2-butylquinoline (4) [27]. The experiment was carried out under N_2 atmosphere. 2-butyl-8-nitroquinoline **2** (1.38 g, 6.1 mmol) was dissolved in 10 mL ethanol. Stannous chloride dihydrate (2.73 g, 10.8 mmol) was added to this solution. The color of the solution turned to yellow orange. This mixture was refluxed at 60°C for 1.5 h. $NaBH_4$ (0.065 mg, 0.61 mmol) was dissolved in 2 mL ethanol and then injected into the reaction mixture. The resulting mixture was refluxed for an additional hour. The reaction mixture was made alkaline with 5–6 mL 40% aqueous NaOH. The color of the mixture changed to gray. Reaction mixture was extracted with 3 × 50 mL ethyl acetate, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford the desired product, 0.14 g (58%); FTIR (v, cm^{-1}): 3296, 2955, 2922, 2852, 1682, 1568, 1520, 1494, 1463, 1456, 1434, 1377, 1311, 1260, 1082, 834, 798, 749; ^{1}H-NMR ($CDCl_3$), δ: 1.01 (t, 3H, J = 7.6 Hz), 1.48 (m, 2H), 1.85 (m, 2H), 2.98 (t, 2H, J = 8.0 Hz), 5.02 (bs, 2H), 6.91 (dd, 1H, J = 7.6, 1.2 Hz), 7.13 (dd, 1H, J = 7.6, 1.2 Hz), 7.24 (d, 1H, J = 8.4 Hz), 7.28 (d, 1H, J = 7.6 Hz), 7.95 (d, 1H, J = 8.0 Hz) ppm; ^{13}C-NMR ($CDCl_3$), δ: 12.99, 21.52, 30.68, 37.55, 108.94, 114.82, 120.60, 125.23, 126.03, 134.94, 136.80, 142.48, 159.04 ppm; HRMS (ESI): (m/z) calcd. for $C_{13}H_{17}N_2$ $[M+H]^+$: 201.1392, found: 201.1283.

2-methylenehexanal (9) [28]. A mixture of hexanal (12 mL, 0.10 mol), dimethylamine hydrochloride (9.85 g, 0.12 mol) and 37% aqueous formaldehyde (9 mL, 0.12 mol) were stirred at 70° C for 20 h. The aqueous phase was separated and extracted with 3 × 60 mL diethyl ether. The combined organic phases were dried over $CaCl_2$, and the solvent was evaporated under reduced pressure. The product was purified by distillation at 70° C/40 mmHg to afford the pure colorless oil, 8.90 g (79%); FTIR (v, cm^{-1}): 3367, 2956, 2931, 2872, 1712, 1592, 1465, 1379, 1093, 960, 731; ^{1}H-NMR ($CDCl_3$), δ: 0.97 (t, 3H), 1.23 (m, 2H), 1.37 (m, 2H), 2.18 (t, 2H), 5.91 (s, 1H), 6.17 (s, 1H), 9.45 (s, 1H) ppm; HRMS (ESI): (m/z) calcd. for $C_7H_{12}O$ $[M+H]^+$: 113.0966, found: 113.0968.

3-butyl-8-nitroquinoline (10) [29]. 2-nitroaniline (4.21 g, 30.5 mmol) and As_2O_5 (3.45 g, 15 mmol) were added to a mixture of H_2SO_4 (1.5 mL H_2SO_4, 0.4 mL H_2O). The mixture was stirred mechanically and heated to 100°C. 2-Methylenehexanal **9** (4.16 mL, 30.5 mmol) was then added slowly without exceeding 120°C. The reaction mixture was refluxed overnight at 110°C. The color of the solution turned to black and its viscosity increased. After cooling, the solution was neutralized with aqueous NaOH. A fraction of the resulting viscous black solid was filtered under vacuum. Both the solid and the aqueous phase were extracted with 3 × 60 mL CH_2Cl_2. The combined organic phases were dried over anhydrous Na_2SO_4. The crude product was purified with silica gel and dichloromethane/hexane (2:1) as the eluent. The pure product was obtained as an orange oil, 2.43 g (35%); FTIR (v, cm^{-1}): 2956, 2929, 2860, 1526, 1465, 1345, 1063, 959, 852, 767; ^{1}H-NMR ($CDCl_3$), δ: 1.00 (t, 3H, J = 7.6 Hz), 1.45 (m, 2H), 1.74 (m, 2H), 2.87 (t, 2H, J = 7.6 Hz), 7.60 (t, 1H, J = 8.0, 7.6 Hz), 7.50 (t, 1H, J = 8.0, 7.6 Hz), 8.0 (m, 3H), 8.76 (d, 1H, J = 2.0 Hz) ppm; ^{13}C-NMR ($CDCl_3$), δ: 13.80, 22.17, 32.79, 32.91, 122.86, 125.20, 129.09, 131.63, 134.03, 137.49, 137.94, 148.15, 154.41 ppm; HRMS (ESI): (m/z) calcd. for $C_{13}H_{15}N_2O_2$ $[M+H]^+$: 253.0953, found: 253.0932.

8-amino-3-butylquinoline (11). The procedure of this experiment is the same as **4**. Brown oily product (85%); FTIR (v, cm^{-1}): 3468, 3371, 2953, 2929, 2858, 1597, 1578, 1499, 1466, 1375, 1342, 1191, 907, 888, 859, 750; ^{1}H-NMR ($CDCl_3$), δ: 0.88 (t, 3H, J = 7.6 Hz), 1.33 (m, 2H), 1.62 (m, 2H), 2.70 (t, 2H, J = 8.0 Hz), 4.90 (bs, 2H), 6.79 (dd, 1H, J = 7.6, 0.8 Hz), 7.02 (dd, 1H, J = 8.0, 1.2 Hz), 7.21 (t, 1H, J = 8.0, 7.6 Hz), 7.75 (d, 1H, J = 2 Hz), 8.54 (d, 1H, J = 2.4 Hz) ppm; ^{13}C-NMR ($CDCl_3$), δ: 13.89, 22.23, 32.86, 33.28, 109.28, 115.65, 127.34, 128.76, 134.13, 135.54, 137.00, 143.827, 149.12 ppm; HRMS (ESI): (m/z) calcd. for $C_{13}H_{17}N_2$ $[M+H]^+$: 201.1392, found: 201.1372.

4-butylquinoline (5). The same procedure as **1** was used. Yellow viscous liquid was obtained (47%); FTIR (v, cm^{-1}): 3033, 2955, 2929, 2870, 1568, 1590, 1508, 1463, 841, 758; ^{1}H-NMR ($CDCl_3$), δ: 0.98 (t, 3H, J = 7.2 Hz), 1.47 (m, 2H), 1.74 (m, 2H), 3.10 (t, 2H, J = 7.6 Hz), 7.38 (d, 1H, J = 4.4 Hz), 7.62 (t, 1H, J = 8.4, 7.6 Hz), 7.96 (dd, 1H, J = 8.0, 0.8 Hz), 8.24 (dd, 1H, J = 8.4, 0.8 Hz), 8.93 (d, 1H, J = 4.4 Hz) ppm; ^{13}C-NMR ($CDCl_3$), δ: 13.77, 22.58, 31.58, 31.92, 120.50, 123.41, 126.00, 127.43, 128.72, 130.06, 148.20, 148.42, 149.96 ppm; HRMS (ESI): (m/z) calcd. for $C_{13}H_{16}N$ $[M+H]^+$: 186.1283, found: 186.1276.

4-butyl-8-nitroquinoline (6). The procedure of this experiment is the same as **2**. Yellowish solid (73%), mp 81°C; FTIR (v, cm^{-1}): 3034, 2957, 2933, 2874, 1594, 1521, 1505, 1471, 1367, 890, 849, 829, 810, 779, 763, 738, 722, 641; ^{1}H-

NMR ($CDCl_3$), δ: 0.94 (t, 3H, J = 7.2 Hz), 1.39 (m, 2H), 1.78 (m, 2H), 2.97 (t, 2H, J = 8.0 Hz), 7.39 (d, 1H, J = 8.8 Hz), 7.50 (t, 1H, J = 8.0, 7.6 Hz), 7.91 (dd, 1H, J = 7.2, 1.2 Hz), 7.95 (dd, 1H, J = 8.4, 1.2 Hz), 8.09 (d, 1H, J = 8.8 Hz) ppm; ^{13}C-NMR ($CDCl_3$), δ: 13.84, 22.64, 32.01, 32.20, 122.35, 122.82, 124.81, 127.62, 128.60, 139.68, 149.20, 152.22 ppm; HRMS (ESI): (m/z) calcd. for $C_{13}H_{15}N_2O_2$ $[M+H]^+$: 231.1134, found: 231.1107.

8-amino-4-butylquinoline (8). The procedure of this experiment is the same as **4** (93%); FTIR (v, cm^{-1}): 3468, 3339, 3033, 2950, 2929, 2869, 1612, 1584, 1516, 1469, 1414, 1363, 1340, 1159, 1102, 840, 818, 743; ^{1}H-NMR ($CDCl_3$), δ: 0.90 (t, 3H, J = 7.6 Hz), 1.37 (m, 2H), 1.66 (m, 2H), 2.94 (t, 2H, J = 7.6 Hz), 4.90 (bs, 2H) 6.84 (dd, 1H, J = 6.4, 2.4 Hz), 7.13 (d, 1H, J = 4.4 Hz), 7.25 (d, 1H, J = 6.8 Hz), 7.27 (d, 1H, J = 4.8 Hz), 8.57 (d, 1H, J = 4.4 Hz) ppm; ^{13}C-NMR ($CDCl_3$), δ: 13.94, 22.78, 32.08, 32.19, 109.69, 111.97, 121.04, 126.88, 128.15, 138.44, 144.54, 147.05, 148.66 ppm; HRMS (ESI): (m/z) calcd. for $C_{13}H_{17}N_2$ $[M+H]^+$: 201.1392, found: 201.1138.

N-(4-butylphenyl)acetamide (12) [30], [31]. In a 50 mL round-bottom flask, 4-butylaniline (4.47 g, 30 mmol) and 9 mL water were added and stirred vigorously. To this reaction mixture, acetic anhydride (4.59 g, 45 mmol) was added. The reaction mixture was stirred at room temperature for 2 h. During this time, a precipitate was observed. The precipitate was filtered and washed with several portions of water and dried under vacuum to give the desired product as khaki solid, 5.21 g (91%), mp 77–80°C; FTIR (v, cm^{-1}): 3250(d), 3186, 3120, 3065, 2954, 2924, 2854, 1660, 1602, 1551, 1510, 1409, 1368, 1320, 1265, 830, 812, 762; ^{1}H-NMR ($CDCl_3$), δ: 0.91 (t, 3H, J = 7.3 Hz), 1.33 (m, 2H), 1.56 (m, 2H), 2.16 (s, 3H), 2.56 (t, 2H, J = 7.6 Hz), 7.12 (d, 2H, J = 8.4 Hz), 7.19 (bs, 1H), 7.37 (d, 2H, J = 8.4 Hz) ppm; ^{13}C-NMR ($CDCl_3$), δ: 13.92, 22.26, 24.50, 33.62, 35.03, 120.01, 128.84, 135.44, 139.05, 168.25 ppm; HRMS (ESI): (m/z) calcd. for $C_{12}H_{18}NO$ $[M+H]^+$: 192.1388, found: 192.1381.

N-(4-butyl-2-nitrophenyl)acetamide (13) [31]: 12. (5.16 g, 26.98 mmol) was dissolved in 6 mL glacial acetic acid. The solution was warmed gently in order to dissolve all the solid material. Then the solution was cooled in an ice bath. To this solution, 7.5 mL concentrated H_2SO_4 was added dropwise at 5°C. Then the nitrating mixture (3 mL concentrated HNO_3 and 3 mL concentrated H_2SO_4) was added in small portions. After the addition of nitrating mixture was finished, the reaction mixture was stirred at room temperature for 50 min. Then, the viscous reaction mixture was poured into a mixture of 50 mL water and 10 g ice. The resulting precipitate was filtered, washed with ice cold water, and dried under vacuum to give a crude product. The crude product was purified with silica gel and CH_2Cl_2 as the eluent to give the pure product as a yellow solid, 6.18 g (97%), mp 46 °C; FTIR (v, cm^{-1}): 3359, 2953, 2927, 2868, 2852, 1698, 1623, 1575, 1510, 1466, 1364, 1331, 1311, 1267, 1253, 1198, 1105, 1037, 854, 680, 581, 524; ^{1}H-NMR ($CDCl_3$), δ: 0.93 (t, 3H, J = 7.3 Hz), 1.35 (m, 2H), 1.60 (m, 2H), 2.27 (s, 3H), 2.63 (t, 2H, J = 7.6 Hz), 7.46 (dd, 1H, J = 8.6, 1.8 Hz), 7.99 (d, 1H, J = 1.8 Hz), 8.62 (d, 1H, J = 8.6 Hz), 10.21 (bs, 1H) ppm; ^{13}C-NMR ($CDCl_3$), δ: 13.85, 22.14, 25.57, 33.10, 34.55, 122.19, 124.87, 132.53, 136.24, 138.55, 168.96 ppm; HRMS (ESI): (m/z) calcd. for $C_{12}H_{16}N_2O_3Na$ $[M+Na]^+$: 259.1059, found: 259.1071.

4-butyl-2-nitroaniline (14) [31]: 13. (1.84 g, 7.8 mmol) was refluxed in 40 mL methanol and 40 mL 20% H_2SO_4 for 2 h. Then, the reaction mixture was cooled to room temperature and made weakly alkaline by slowly adding a 5% aqueous $NaHCO_3$. The resulting solution was extracted with 2 × 50 mL diethyl ether. The ether layers were combined, washed with water, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The pure orange liquid product was obtained, 1.45 g (96%), mp 259 °C; FTIR (v, cm^{-1}): 3490, 3370, 2956, 2928, 2858, 1634, 1590, 1515, 1466, 1410, 1337, 1246, 1190, 1168, 1094, 824, 767; ^{1}H-NMR ($CDCl_3$), δ: 0.92 (t, 3H, J = 7.3 Hz), 1.33 (m, 2H), 1.55 (m, 2H), 2.52 (t, 2H, J = 7.6 Hz), 5.94 (bs, 2H), 6.73 (d, 1H, J = 8.5 Hz), 7.19 (dd, 1H, J = 8.5, 2.0 Hz), 7.90 (d, 1H, J = 1.6 Hz) ppm; ^{13}C-NMR ($CDCl_3$), δ: 13.87, 22.12, 33.26, 34.17, 118.76, 124.71, 131.79, 136.55, 142.91 ppm; HRMS (ESI): (m/z) calcd. for $C_{10}H_{15}N_2O_2$ $[M+H]^+$: 195.1134, found: 195.1131.

1-butyl-3-nitrobenzene (15) [32]. In a 50 mL round-bottom flask, **14** (0.767 g, 3.25 mmol) was dissolved in 15 mL acetic acid. To this solution, 6.5 g ice was added, and the resulting suspension was cooled to 0°C. A solution of sodium nitrite (0.246 g, 3.58 mmol) in water (1 mL) was added dropwise, and the reaction mixture was stirred at 0°C for 30 min. The resulting clear solution of the diazo salt was added dropwise to a solution of $FeSO_4.7H_2O$ (0.904 g, 3.25 mmol) in dimethylformamide (11 mL) pre-cooled to 0°C. The reaction mixture was allowed to warm to room temperature and stirred for additional 30 min, diluted with water (100 mL), and the product was extracted into dichloromethane (3 × 40 mL). The organic phase was washed with a 10% aqueous NaOH (3 x 30 mL), dried (Na_2SO_4), and evaporated. In order to remove DMF, the product was again extracted with water/diethyl ether (10:1) mixture, and combined organic phases were evaporated. The resulting crude product was purified through a column chromatography using silica gel and hexane as eluent phase. Solvent was evaporated to afford a yellowish liquid, 264 mg (41%); FTIR (v, cm^{-1}): 2958, 2931, 2861, 1524, 1348, 1098, 1086, 804, 790, 731, 685, 672; ^{1}H-NMR ($CDCl_3$), δ: 0.94 (t, 3H, J = 7.2 Hz), 1.38 (m, 2H), 1.63 (m, 2H), 2.71 (t, 2H, J = 7.6 Hz), 7.44 (dd, 1H, J = 8.4, 1.2 Hz), 7.49 (d, 1H, J = 7.2 Hz), 8.02 (d, 1H, J = 1.2 Hz), 8.04 (bs, 1H) ppm; ^{13}C-NMR ($CDCl_3$), δ: 12.81, 21.18, 32.20, 34.25, 119.83, 122.17, 128.04, 133.72, 143.81, 147.35 ppm; HRMS (ESI): (m/z) calcd. for $C_{10}H_{14}NO_2$ $[M+H]^+$: 180.1025, found: 180.1022.

3-butylaniline (16). The procedure of this experiment is the same as **4**. Yellow liquid was obtained (95%); FTIR (v, cm^{-1}): 3306, 2955, 2928, 2858, 1677, 1605, 1591, 1488, 1441, 1377, 1311, 1260, 1167, 1105, 776, 696; ^{1}H-NMR ($CDCl_3$), δ: 0.93 (t, 3H, J = 7.6 Hz), 1.37 (m, 2H), 1.58 (m, 2H), 2.53 (t, 2H, J = 7.6 Hz), 3.36 (bs, 2H), 6.52 (d, 1H, J = 8.0 Hz), 6.54 (s, 1H), 6.60 (d, 1H, J = 7.6 Hz), 7.07 (t, 1H, J = 7.6 Hz) ppm; ^{13}C-NMR ($CDCl_3$), δ: 13.96, 22.41, 33.52, 35.64, 112.59, 115.38, 118.98, 129.11, 144.22, 146.12 ppm; HRMS (ESI): (m/z) calcd. for $C_{10}H_{16}N$ $[M+H]^+$: 150.1283, found: 150.1278.

5-butylquinoline (17) and 7-butylquinoline (18) [33]. In a 100 mL 3-necked round-bottom flask was placed **16** (7.69 g, 51.5 mmol), glycerol (5.7 mL, 78 mmol) and iodine (0.24 g, 1.9 mmol). The reaction mixture was stirred, and 8 mL concentrated H_2SO_4 was added down the condenser. Reaction soon commenced, the temperature raised to 100–105°C. The flask was heated gradually, with stirring, in a silicone bath to 140°C; the reaction proceeded with the evolution of sulfur dioxide and some iodine vapor. Heating at 170°C was continued for 2.5 h. Reaction was monitored by TLC. When the reaction was complete, it was cooled and made alkaline by using 5 N aqueous NaOH. The resulting mixture was extracted

using dichloromethane (3 × 100 mL), dried over anhydrous Na_2SO_4 and filtered. Solvent was removed on a rotary evaporator. The crude products were subjected to column chromatography using silica and different solvent mixtures, but the vast majority of the products were inseparable. In order to identify the structures of 5-butylquinoline **17** and 7-butylquinoline **18**, a small amount of mixture was separated by analytical chromatography on silica TLC plates. The amount of 5-butylquinoline **17** was just enough to obtain ^{1}H-NMR. Because it was difficult to separate isomers, the mixture of products was nitrated at the next step, 6.82 g (72%); regioisomeric ratio 1:4.

5-butylquinoline (17). ^{1}H-NMR ($CDCl_3$), δ: 0.85 (t, 3H, J = 7.6 Hz), 1.33 (m, 2H), 1.58 (m, 2H), 2.92 (t, 2H, J = 7.6 Hz), 7,25 (d, 1H, J = 6.8 Hz), 7.28 (t, 1H, J = 8.0, 4.0 Hz), 7.50 (dd, 1H, J = 8.4, 6.8 Hz), 7.87 (d, 1H, J = 8.8 Hz), 8.23 (dd, 1H, J = 8.0, 1.6 Hz), 8.78 (dd, 1H, J = 4.0, 1.6 Hz) ppm; HRMS (ESI): (m/z) calcd. for $C_{13}H_{16}N$ $[M+H]^+$: 186.1283, found: 186.1263.

7-butylquinoline (18). FTIR (v, cm^{-1}): 3049, 2955, 2928, 2858, 1625, 1596, 1501, 1450, 1317, 833, 769, 730, 614, 477; ^{1}H-NMR ($CDCl_3$), δ: 0.94 (t, 3H, J = 7.2 Hz), 1.39 (m, 2H), 1.70 (m, 2H), 2.82 (t, 2H, J = 7.6 Hz), 7,32 (dd, 1H, J = 8.4, 4.4 Hz), 7.38 (dd, 1H, J = 8.4, 1.6 Hz), 7.71 (d, 1H, J = 8.4 Hz), 7.88 (s, 1H), 8.09 (dd, 1H, J = 8.0, 1.2 Hz), 8.67 (dd, 1H, J = 4.0, 1.6 Hz) ppm; ^{13}C-NMR ($CDCl_3$), δ: 13.92, 22.29, 33.14, 35.80, 120.29, 126.55, 127.44, 127.73, 128.21, 135.78, 144.70, 148.43, 150.23 ppm; HRMS (ESI): (m/z) calcd. for $C_{13}H_{16}N$ $[M+H]^+$: 186.1283, found: 186.1263.

Nitration of 5-butylquinoline (17) and 7-butylquinoline (18) mixture. To a mixture of **17** and **18** (6.82 g, 36.81 mmol) in 15.5 mL concentrated H_2SO_4, cooled in an iced bath was added dropwise 12.5 mL of concentrated H_2SO_4/HNO_3 mixture (3:1). Reaction was maintained at 0°C, stirred rapidly and monitored by TLC until all the quinoline was consumed (2.5 h). Mixture was diluted with 50 mL water, and NaOH(s) was added until pH 10–11. Solution was extracted with 3 × 100 mL CH_2Cl_2, dried over anhydrous Na_2SO_4, filtered and evaporated. Nitration of **17** and **18** resulted in 5-butyl-8-nitroquinoline **20**, 5-butyl-6-nitroquinoline **19**, and 7-butyl-8-nitroquinoline **21**. In order to separate the mixture of isomers, the column was prepared using silica gel and dichloromethane/hexane (3:1) as the eluent phase. 5-butyl-8-nitroquinoline **20**, 1.13 g (13%); 5-butyl-6-nitroquinoline **19**, 0.1 g (1.2%); 7-butyl-8-nitroquinoline **21**, 7.45 g (86%); overall nitration yield: 90%.

5-butyl-8-nitroquinoline (20). mp 73°C; FTIR (v, cm^{-1}): 3079, 2954, 2927, 2868, 2359, 1574, 1515, 1468, 1397, 836, 797, 773, 740, 635, 613, 487; ^{1}H-NMR ($CDCl_3$), δ: 0.98 (t, 3H, J = 7.6 Hz), 1.46 (m, 2H), 1.71 (m, 2H), 3.10 (t, 2H, J = 8.0 Hz), 7.42 (d, 1H, J = 7.6 Hz), 7.55 (dd, 1H, J = 8.4, 4.0 Hz), 7.94 (d, 1H, J = 7.6 Hz), 8.43 (dd, 1H, J = 8.8, 1.6 Hz), 9.05 (dd, 1H, J = 4.4, 1.6 Hz) ppm; ^{13}C-NMR ($CDCl_3$), δ: 13.81, 22.62, 32.32, 32.94, 122.19, 123.49, 124.74, 132.44, 140.03, 144.90, 146.91, 151.91 ppm; HRMS (ESI): (m/z) calcd. for $C_{13}H_{15}N_2O_2$ $[M+H]^+$: 231.1134, found: 231.1126.

5-butyl-6-nitroquinoline (19). mp 62°C; FTIR (v, cm^{-1}): 2958, 2930, 2872, 1522, 1495, 1464, 1353, 1328, 877, 838, 812, 797, 770, 746, 542; ^{1}H-NMR ($CDCl_3$), δ: 1.00 (t, 3H, J = 7.6 Hz), 1.55 (m, 2H), 1.75 (m, 2H), 3.18 (t, 2H, J = 8.0 Hz), 7.57 (dd, 1H, J = 8.4, 4.0 Hz), 7.99 (d, 1H, J = 9.2 Hz), 8.05 (d, 1H, J = 9.2 Hz), 8.50 (dd, 1H, J = 8.8, 0.8 Hz), 9.03 (dd, 1H, J = 4.4, 1.6 Hz) ppm; ^{13}C-NMR ($CDCl_3$), δ: 13.75, 23.13, 27.76, 33.27, 122.34, 124.02, 127.00, 129.34, 133.97, 135.01, 149.26, 152.31 ppm; HRMS (ESI): (m/z) calcd. for $C_{13}H_{15}N_2O_2$ $[M+H]^+$: 231.1134, found: 231.1128.

7-butyl-8-nitroquinoline (21). mp 42°C; FTIR (v, cm^{-1}): 2957, 2930, 2872, 1598, 1529, 1497, 1457, 1376, 1354, 1315, 876, 838, 799, 642; ^{1}H-NMR ($CDCl_3$), δ: 0.92 (t, 3H, J = 7.2 Hz), 1.39 (m, 2H), 1.68 (m, 2H), 2.75 (t, 2H, J = 7.6 Hz), 7.44 (d, 1H, J = 8.0 Hz), 7.46 (t, 1H, J = 8.0, 4.4 Hz), 7.84 (d, 1H, J = 8.8 Hz), 8.16 (dd, 1H, J = 8.8, 1.6 Hz), 8.93 (dd, 1H, J = 4.4, 1.6 Hz) ppm; ^{13}C-NMR ($CDCl_3$), δ: 13.77, 22.53, 31.34, 32.67, 122.11, 126.91, 127.91, 129.24, 134.76, 135.62, 139.67, 148.10, 152.06 ppm; HRMS (ESI): (m/z) calcd. for $C_{13}H_{15}N_2O_2$ $[M+H]^+$: 231.1134, found: 231.1106.

8-amino-5-butylquinoline (22). The procedure of this experiment is the same as **4** (96.4%); FTIR (v, cm^{-1}): 3465, 3353, 2953, 2927, 2857, 1610, 1587, 1506, 1477, 1365, 1336, 821, 785; ^{1}H-NMR ($CDCl_3$), δ: 0.97 (t, 3H, J = 7.6 Hz), 1.44 (m, 2H), 1.66 (m, 2H), 2.92 (t, 2H, J = 7.6 Hz), 4.87 (bs, 2H) 6.86 (d, 1H, J = 7.6 Hz), 7.16 (d, 1H, J = 7.6 Hz), 7.35 (dd, 1H, J = 8.8, 4.4 Hz), 8.26 (dd, 1H, J = 8.8, 1.6 Hz), 8.78 (dd, 1H, J = 4.4, 1.6 Hz) ppm; ^{13}C-NMR ($CDCl_3$), δ: 14.06, 22.73, 31.54, 33.45, 109.89, 120.77, 126.90, 127.28, 132.43, 138.97, 142.28, 146.82 ppm; HRMS (ESI): (m/z) calcd. for $C_{13}H_{17}N_2$ $[M+H]^+$: 201.1392, found: 201.1376.

8-amino-7-butylquinoline (23). The procedure of this experiment is the same as **4** (75%); FTIR (v, cm^{-1}): 3478, 3370, 3050, 2954, 2927, 2858, 1586, 1558, 1504, 1456, 1371, 1105, 822, 798, 673; ^{1}H-NMR ($CDCl_3$), δ: 1.00 (t, 3H, J = 7.6 Hz), 1.47 (m, 2H), 1.71 (m, 2H), 2.71 (t, 2H, J = 7.2 Hz), 5.02 (bs, 2H), 7.13 (d, 1H, J = 8.4 Hz), 7.28 (d, 1H, J = 8.4 Hz), 7.30 (t, 1H, J = 8.0, 4.0 Hz), 8.01 (d, 1H, J = 8.4 Hz), 8.77 (d, 1H, J = 4.0 Hz) ppm; ^{13}C-NMR ($CDCl_3$), δ: 14.10, 22.85, 31.01, 31.44, 115.44, 120.44, 122.74, 127.15, 129.16, 135.82, 138.43, 140.71, 147.37 ppm; HRMS (ESI): (m/z) calcd. for $C_{13}H_{17}N_2$ $[M+H]^+$: 201.1392, found: 201.1367.

6-butylquinoline (24). The procedure of this experiment is the same as with **17** and **18** (59%); FTIR (v, cm^{-1}): 3013, 2955, 2927, 2856, 1499, 1464, 1377, 1118, 833, 796, 770, 615, 478; ^{1}H-NMR ($CDCl_3$), δ: 0.86 (t, 3H, J = 7.2 Hz), 1.31 (m, 2H), 1.60 (m, 2H), 2.69 (t, 2H, J = 7.6 Hz), 7.23 (dd, 1H, J = 8.4, 4.4 Hz), 7.46 (m, 2H), 7.93 (d, 1H, J = 9.2 Hz), 7.95 (d, 1H, J = 8.4 Hz), 8.74 (dd, 1H, J = 4.4, 1.6 Hz) ppm; ^{13}C-NMR ($CDCl_3$), δ: 12.89, 21.32, 32.33, 34.55, 119.96, 124.96, 127.30, 128.13, 130.03, 134.48, 140.27, 146.07, 148.47 ppm; HRMS (ESI): (m/z) calcd. for $C_{13}H_{16}N$ $[M+H]^+$: 186.1283, found: 186.1278.

6-butyl-5-nitroquinoline (25). The procedure of this experiment is the same as with **3**. Brown viscous liquid (62%); FTIR (v, cm^{-1}): 2958, 2931, 2872, 1522, 1495, 1464, 1353, 1328, 877, 838, 812, 797, 770, 746, 542; ^{1}H-NMR ($CDCl_3$), δ: 0.83 (t, 3H, J = 7.2 Hz), 1.29 (m, 2H), 1.59 (m, 2H), 2.67 (t, 2H, J = 7.6 Hz), 7.42 (dd, 1H, J = 8.0, 4.4, 1.6 Hz), 7.52 (d, 1H, J = 8.8 Hz), 7.93 (d, 1H, J = 8.8 Hz), 8.06 (d, 1H, J = 8.8 Hz), 8.84 (dd, 1H, J = 4.4, 1.6 Hz) ppm; ^{13}C-NMR ($CDCl_3$), δ: 13.75, 22.52, 31.54, 32.75, 120.22, 123.05, 130.00, 130.79, 132.18, 133.25, 146.36, 146.54, 150.93 ppm; HRMS (ESI): (m/z) calcd. for $C_{13}H_{15}N_2O_2$ $[M+H]^+$: 231.1134, found: 231.1123.

5-bromo-6-butylquinoline (27) [34]: 24. (3.42 g, 18.4 mmol) was slowly added to 18.4 mL concentrated H_2SO_4 dropwise. The exothermic reaction was kept below 30°C, then the solution was cooled to −40°C, and N-bromosuccinimide (NBS) (3.83 g, 21.5 mmol) was slowly added to this solution piecewise while the temperature was kept around −40°C. The suspension was stirred at 0°C for 1 h. Then the mixture was

poured onto 100 g of crushed ice, and 25% aqueous NH_3 was added until pH = 9 while the temperature was kept under 25°C. The mixture was then extracted with diethyl ether. The organic phase was washed first with 15% aqueous NaOH and then twice with distilled water and dried over Na_2SO_4. The resulting mixture was filtered and evaporated. The crude product was purified first by crystallization, where it was initially dissolved in 3–4 mL dichloromethane, and then 100 mL of petroleum ether was added and the resulting solution was placed in a refrigerator. After crystallization, the product was separated by a column chromatography on silica gel using dichloromethane/hexane (1:3) as eluent to afford pure orange-yellow solid **27**, 4.47 g, (92%) mp 51–54°C; FTIR (v, cm^{-1}): 2955, 2927, 2859, 1522, 1492, 1456, 962, 906, 832, 804, 767; ^{1}H-NMR ($CDCl_3$), δ: 0.75 (t, 3H, J = 7.6 Hz), 1.19 (m, 2H), 1.39 (m, 2H), 2.67 (t, 2H, J = 8.0 Hz), 7.12 (dd, 1H, J = 8.8, 4.4 Hz), 7.26 (d, 1H, J = 8.8 Hz), 7.76 (d, 1H, J = 8.8 Hz), 8.26 (dq, 1H, J = 8.8, 1.6 Hz), 8.60 (dd, 1H, J = 4.4, 1.6 Hz) ppm; ^{13}C-NMR ($CDCl_3$), δ:13.92, 22.51, 32.08, 36.74, 121.90, 122.35, 127.97, 128.71, 131.39, 135.40, 140.91, 147.57, 149.82 ppm; HRMS (ESI): (m/z) calcd. for $C_{13}H_{15}^{79}BrN$ $[M+H]^+$: 264.0388, found: 264.0352.

5-bromo-6-butyl-8-nitroquinoline (29). The procedure of this experiment is the same as **3**. Yellowish solid (85%); FTIR (v, cm^{-1}): 3069, 2953, 2931, 2869, 1552, 1525, 1493, 1456, 1371, 1340, 1020, 966, 909, 891, 780, 729; ^{1}H-NMR ($CDCl_3$), δ: 0.99 (t, 3H, J = 7.2 Hz), 1.46 (m, 2H), 1.71 (m, 2H), 3.03 (t, 2H, J = 8.0 Hz), 7.63 (dd, 1H, J = 8.8, 4.0 Hz), 7.94 (s, 1H), 8.70 (dd, 1H, J = 8.8, 1.6 Hz), 9.02 (dd, 1H, J = 4.0, 1.6 Hz) ppm; ^{13}C-NMR ($CDCl_3$), δ: 13.86, 22.50, 31.82, 36.77, 123.71, 125.23, 126.58, 128.85, 136.01, 138.66, 140.75, 147.33, 152.05 ppm; HRMS (ESI): (m/z) calcd. for $C_{13}H_{14}^{79}BrN_2O_2$ $[M+H]^+$: 309.0239, found: 309.0251.

8-amino-6-butylquinoline (30). The procedure of this experiment is the same as **5**. Dark green liquid (77%); FTIR (v, cm^{-1}): 3467, 3347, 3030, 2954, 2927, 2857, 1618, 1588, 1502, 1431, 1380, 841, 785; ^{1}H-NMR ($CDCl_3$), δ: 0.96 (t, 3H, J = 7.6 Hz), 1.41 (m, 2H), 1.68 (m, 2H), 2.68 (t, 2H, J = 8.0 Hz), 4.60 (bs, 2H) 6.80 (d, 1H, J = 1.6 Hz), 6.95 (s, 1H), 7.32 (dd, 1H, J = 8.8, 4.4 Hz), 7.97 (dd, 1H, J = 8.4, 1.6 Hz), 8.70 (d, 1H, J = 4.0, 1.2 Hz) ppm; ^{13}C-NMR ($CDCl_3$), δ: 13.97, 22.40, 33.36, 36.02, 111.57, 114.84, 121.30, 128.88, 135.49, 142.31, 143.49, 146.59 ppm; HRMS (ESI): (m/z) calcd. for $C_{13}H_{16}N_2$ $[M+H]^+$: 201.1392, found: 201.1149.

Acknowledgments. This work was financially supported by Bogazici University Scientific Research Funds (BAP, Project No: 5085) and TUBITAK (Project No: 109T431).

REFERENCES AND NOTES

[1] Fox, R. I. Semin Arthritis Rheum 1993, 23, 82.

[2] Tilley, L.; Loria, P.; Foley, M. In Antimalarial Chemotherapy; Rosenthal, P. J., Ed.; Humana Press: Totowa, New Jersey, 2001; Vol 47, pp 87–121.

[3] Savarino, A.; Gennero, L.; Chen, H. C.; Serrano, D.; Malavasi, F.; Boelaert, J. R.; Sperber, K. AIDS 2001, 15, 2221.

[4] Ni-Komatsu, L.; Tong, C.; Chen, G.; Brindzei, N.; Orlow, S. Mol Pharmacol 2008, 74, 1576.

[5] Edgcomb, J. H.; Arnold, J.; Yount, E. H.; Alving, A. S.; Eichelberger, L.; Jeffery, G. M.; Eyles, D.; Young, M. D. J Natl Malar Soc 1950, 9, 285.

[6] Loeb, F.; Clark, W. M.; Coatney, G. R.; Coggeshall, L. T.; Dieuaide, F. R.; Dochez, A. R.; Hakansson, E. G.; Marshall, E. K.; Marvel, C. S.; McCoy, O. R.; Sapero, J. J.; Sebrell, W. H.; Shannon, J. A.; Carden, G. A. J Am Med Assoc 1946, 130, 1069.

[7] Finley, K. T. In Kirk-Othmer Encyclopedia of Chemical Technology, 5th ed.; Seidel A., Ed.; Wiley: New Jersey, 2006; Vol 21, pp 182–214.

[8] Kim, J. L.; Kim, J. K.; Hong, S. I. Polym Bull 1999, 42, 511.

[9] Economopoulos, S. P.; Chochos, C. L.; Gregoriou, V. G.; Kallitsis, J. K.; Barrau, S.; Hadziioannou, G. Macromol (Washington, DC, US) 2007, 40, 921.

[10] Ma, Z.; Ding, J.; Cheng, Y.; Xie, Z.; Wang, L.; Jing, X.; Wang, F. Polymer 2011, 52, 2189.

[11] Xue, G.; Bradshaw, J. S.; Dalley, N. K.; Savage, P. B.; Krakowiak, K. E.; Izatt, R. M.; Prodi, L.; Montalti, M.; Zaccheroni, N. Tetrahedron 2001, 57, 7623.

[12] Cywinski, P.; Sadovska, M.; Danel, A.; Buma, W. J.; Brouwer, A. M. J Appl Polym Sci 2007, 105, 229.

[13] Foley, M.; Tilley, N. Pharmacol Ther 1998, 79, 55; (b) Charpentier, P.; Lobregat, V.; Levacher, V.; Dupas, G.; Queguiner, G.; Bourguignon, J. Tetrahedron Lett 1998, 39, 4013; (c) Ranu, B. C.; Hajra, A.; Dey, S. S.; Jana, U. Tetrahedron 2003, 59, 813; (d) Jia, C. S.; Zhang, Z.; Tu, S. J.; Wang, G. W. Org Biomol Chem 2006, 4, 104; (e) Martinez, R.; Ramon, D. J.; Yus, M. Eur J Org Chem 2007, 1599; (f) Arcadi, A.; Marinelli, F.; Rossib, E. Tetrahedron 1999, 55, 13233; (g) Amii, H.; Kishikawa, Y.; Uneyama, K. Org Lett 2001, 3, 1109.

[14] Solomon, V. R.; Lee, H. Curr Med Chem 2011, 18, 1488.

[15] Nycz, J. E.; Szala, M.; Malecki, G. J.; Nowak, M.; Kusz, J. Spectrochim Acta A 2014, 117, 351.

[16] Cinelli, M. A.; Li, H.; Chreifi, G.; Martasek, P.; Roman, L. J.; Poulos, T. L.; Silverman, R. B. J Med Chem 2014, 57, 1513.

[17] Fotie, J.; Wangun, H. V. K.; Fronczek, F. R.; Maasawe, N.; Bhattarai, B. T.; Rhodus, J. L.; Singleton, T. A.; Bohle, D. S. J Org Chem 2012, 77, 2784.

[18] Laras, Y.; Hugues, V.; Chandrasekaran, Y.; Blanchard-Desce, M.; Acher, F. C.; Pietrancosta, N. J Org Chem 2012, 77, 8294.

[19] Queener, S. F.; Bartlett, M. S.; Nasr, M.; Smith, J. W. Antimicrob Agents Chemother 1993, 37, 2166.

[20] Inouye, Y.; Matsumoto, H.; Morishige, R.; Kitahara, Y.; Kubo, A.; Nakamura, S. Chem Pharm Bull 1991, 39, 994.

[21] Hamann, L. G.; Mani, N. S.; Davis, R. L.; Wang, X. J Med Chem 1999, 42, 210.

[22] Pieringer, A. P.; Newhall, W. F. J Agric Food Chem 1968, 16, 523.

[23] Kouznetsov, V. V.; Vargas Mendez, L. Y.; Melendez Gomez, C. M. Curr Org Chem 2005, 9, 141.

[24] Alajarin, R.; Burgos, C. Mod Heterocycl Chem 2011, 3, 1527.

[25] Gomtsyan, A.; Bayburt, E. K.; Schmidt, R. G.; Zheng, G. Z.; Perner, R. J.; Didomenico, S.; Koenig, J. R.; Turner, S.; Jinkerson, T.; Drizin, I.; Hannick, S. M.; Macri, B. S.; McDonald, H. A.; Honore, P.; Wismer, C. T.; Marsh, K. C.; Wetter, J.; Stewart, K. D.; Oie, T.; Jarvis, M. F.; Surowy, J. S.; Faltynek, C. R.; Lee, C. H. J Med Chem 2005, 48, 744.

[26] Doherty, S.; Robins, E. G.; Pál, I.; Newman, C. R.; Hardacre, C.; Rooney, D.; Mooney, D. A. Tetrahedron: Asymmetry 2003, 14, 1517.

[27] Ghosh, B.; Antonio, T.; Zhen, J.; Kharkar, P.; Reith, M. R. A.; Dutta, A. K. J Med Chem 2010, 53, 1023.

[28] Ragoussis, V.; Giannikopoulos, A.; Skoka, E.; Grivas, P. J Agric Food Chem 2007, 55, 5050.

[29] Pomeranc, D.; Heitz, V.; Chambron, J. C.; Sauvage, J. P. J Am Chem Soc 2001, 123, 12215.

[30] Bose, A. K.; Manhas, M. S.; Pednekar, S.; Ganguly, S. N.; Dang, H.; He, W.; Mandadi, A. Tetrahedron Lett 2005, 46, 1901.

[31] Buszek, K. R.; Brown, N.; Luo, D. Org Lett 2009, 11, 201.

[32] Malkov, A. V.; Figlus, M.; Stoncius, S.; Kocovsky, P. J Org Chem 2007, 72, 1315.

[33] Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R. Vogel's Textbook of Practical Organic Chemistry, 5th ed.; Longman: Harlow, 1989; pp 1185–1186.

[34] Offner, J. D.; Schnakenburg, G.; Rose-Munch, F.; Rose, E.; Dötz, K. H. Organometallics 2010, 29, 3308.