

Article

A Convenient One-Pot Preparation of 2-Methyl-3-(phenylthio-methyl)quinolines from Morita-Baylis-Hillman Adducts and Their Oxidation to the Corresponding Sulfones

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Abstract: A convenient one-pot preparation of 2-methyl-3-(phenylthiomethyl)quinolines from Morita-Baylis-Hillman adducts via conjugate addition of thiols followed by reductive cyclization with Fe/AcOH was developed. The 2-methyl-3-(phenylthiomethyl)quinolines were transformed into 2-methyl-3-(phenylsulfonylmethyl)quinolines via *m*-CPBA-mediated oxidation.

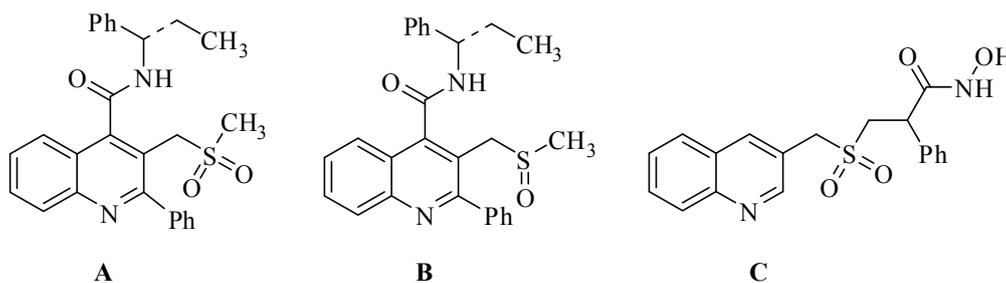
Keywords: one-pot procedure; Morita-Baylis-Hillman adducts; quinolines; reductive cyclization; Fe/AcOH

1. Introduction

The quinoline nucleus is a ubiquitous heterocyclic structural motif that is found in many naturally occurring quinoline alkaloids, therapeutic and synthetic compounds with a wide spectrum of biological activities such as antimalarial, antidiabetic, anti-inflammatory, antiasthmatic, antihypertensive, antibacterial, tyrosine kinase inhibiting agents [1–4]. Quinoline and their derivatives have been utilized for the construction of nano- and meso structures having enhanced electronic and photonic properties [5]. In particular, the C3-alkylsulfone-containing quinolines possess important biological activities. Some of the important C3-alkylsulfonyl and C3-alkylsulfoxide quinoline derivatives are depicted in Figure 1 [6,7]. Compound **A** displayed excellent functional activity, compound **B** exhibits excellent *in vivo/in vitro* DMPK profile and acts as potent NK3 receptor antagonists [6]. Similarly, compound **C** acts as

inhibitor of soluble human CD23 [7]. In this regard, C3-alkylthioquinoline derivatives are key precursors for the preparation of C3-alkylsulfonylquinoline derivatives. The C3-alkylthioquinolines are easily transformed into the corresponding C3-alkylsulfonylquinolines via oxidation reactions. Many protocols have been developed for the synthesis of quinoline derivatives [8–18]. However, the synthesis of C3-alkylthioquinoline and their derivatives are very rare [6]. Therefore, an easy and simple synthesis of C3-alkylthioquinolines and their derivatives is still needed.

Figure 1. Biologically important C3-alkylsulfonyl or C3-alkylsulfoxide quinoline derivatives.



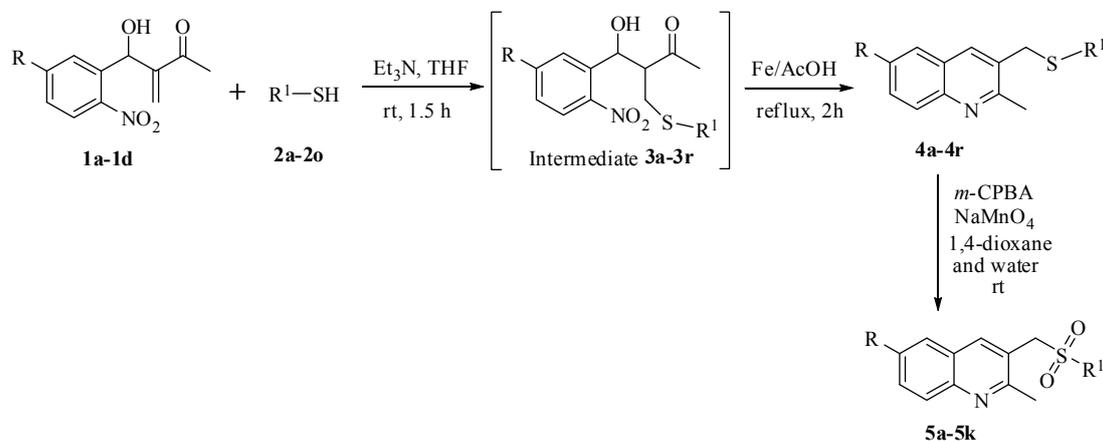
The Morita-Baylis-Hillman (MBH) reaction is a useful carbon-carbon bond forming reaction, which has the propensity to afford densely functionalized adducts [19–21]. Thiol addition to Morita-Baylis-Hillman adducts is well explored in the literature [22–25]. However, to our knowledge, the synthesis of C3-alkylthioquinolines and their derivatives from the MBH adducts is not known. Recently, Kim *et al.* attempted the synthesis of C3-arylthiomethylquinoline derivatives from (*Z*)-methyl 3-(2-azidophenyl)-2-(phenylthiomethyl)acrylate (MBH adduct) using the aza-Wittig reaction, but they failed to obtain the desired product, obtaining instead methylquinoline-3-carboxylate. However, they obtained phenylsulfinylmethyl-containing quinolines from MBH adducts by the aza-Wittig reaction in a multi-step synthetic route [22]. As part of our ongoing project on the synthesis of nitrogen-containing heterocyclic molecules via reductive cyclization [26–30], herein, we wish to report a convenient one-pot procedure for the preparation of C3-arylthiomethylquinolines from the MBH adducts and the transformation of the reaction products into the corresponding C3-arylsulfonylmethyl-containing quinoline derivatives via an oxidation reaction.

2. Results and Discussion

Recently, we developed an easily accessible method for the synthesis of indolylquinoline derivatives from MBH adducts [26]. Taking cues from this reaction, we envisioned synthesizing C3-arylthiomethylquinoline derivatives from MBH adducts derived from the reaction of 2-nitrobenzaldehydes and methyl vinyl ketone. Our synthetic strategy for accessing 2-methyl-3-(phenylsulfonylmethyl)quinoline derivatives is outlined in Scheme 1. The starting MBH adducts were prepared according to a previously reported procedure [31]. Initially, the MBH adduct **1a** was treated with benzenethiol **2a** in the presence of triethylamine in THF at room temperature to yield intermediate compound **3a**, which was treated with Fe/AcOH heated under reflux conditions to give the corresponding 2-methyl-3-(phenylthiomethyl)quinoline compound **4a**. Subsequently, sulfide **4a** was subjected to oxidation with a stoichiometric amount of 3-chloroperoxybenzoic acid (*m*-CPBA) and sodium permanganate in 1,4-dioxane/water (1:1) at room temperature for 20 min, to provide the

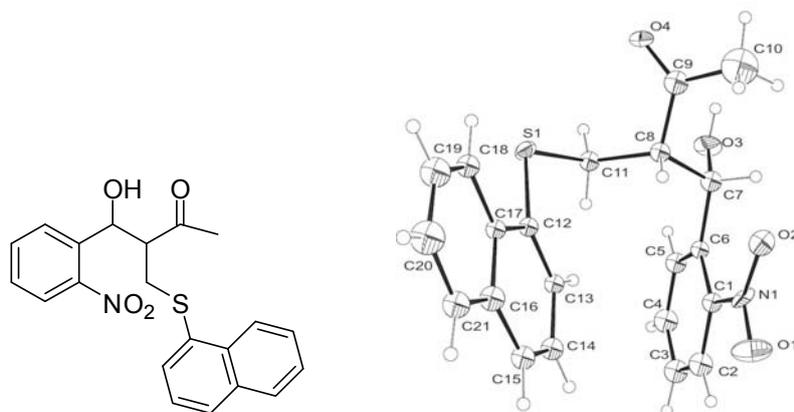
expected the 2-methyl-3-(phenylsulfonylmethyl)quinoline compound **5a**. The first two steps of Scheme 1 were conducted in a one-pot operation.

Scheme 1. Outline of our synthetic route for the synthesis of 2-methyl-3-(phenylthiomethyl)quinoline derivatives and 2-methyl-3-(phenylsulfonylmethyl)quinoline derivatives.



A literature survey revealed that the addition of thiols to MBH acetates takes place either at the γ -position via a S_N2' reaction [22–25] or mixture of the products [major product at γ -position ($E/Z = 10:1$) and trace amount of product at α -position] [25]. In order to determine the structure of the intermediates **3a–3r** in our process, we conducted the reaction of MBH adduct **1a** with naphthalene thiol **2h** in the presence of triethylamine. The intermediate **3h** obtained from this reaction was isolated and analysed by the ^1H - and ^{13}C -NMR, which revealed that the intermediate **3h** formed is 4-hydroxy-3-((naphthalen-1-ylthio)methyl)-4-(2-nitrophenyl)butan-2-one and it is obtained as mixture of diastereomers. When it was subjected to crystallization, the major diastereomer (with the relative configuration $7S^*$ and $8S^*$) was crystallized out. The structure of the major diastereomer was confirmed by single crystal X-ray diffraction analysis (Figure 2).

Figure 2. Crystal structure of the 4-hydroxy-3-((naphthalen-1-ylthio)methyl)-4-(2-nitrophenyl)butan-2-one intermediate **3h** (relative configuration is $7S^*$ and $8S^*$) [32].

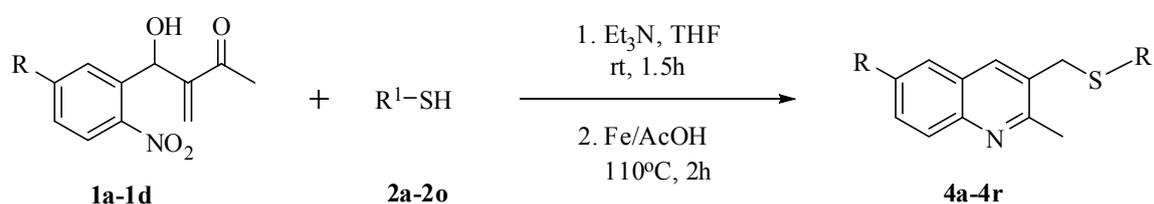


Hence it is quite clear that the intermediate **3h** obtained from the reaction of MBH alcohol and thiol is a conjugate adduct, which is different from the product from the reaction of MBH acetate and

thiol [22–25]. However, our main aim was the synthesis of 2-methyl-3-(phenylthiomethyl)quinoline derivatives **4a–r** in a one-pot operation, therefore without further isolation of other intermediates **3a–r** (tetrahydrofuran solvent was simply removed under reduced pressure) we carried out the next step to obtain the 2-methyl-3-(phenylthiomethyl)quinoline derivatives **4a–r**.

The results presented in Table 1 reveal that thiophenol, thionaphthol and thiophenols containing alkyl, methoxy and halo substituents in the phenyl ring smoothly furnished the corresponding alkyl and arylthiomethylquinolines **4a–r** in 64–75% yields. There was no significant effect of the nature of the substituents on the yields of the products. All the products were fully characterized by ^1H - and ^{13}C -NMR as well as LR and HRMS.

Table 1. One-pot synthesis of 2-methyl-3-(phenylthiomethyl)quinolines and their derivatives from Morita-Baylis-Hillman adducts.



Entry	MBH adduct 1	R	R ¹	Thiol 2	Product 4	Yield(%) ^{a,b}
1	1a	H	C ₆ H ₅	2a	4a	66
2	1a	H	4-OMe-C ₆ H ₄	2b	4b	69
3	1a	H	4-Br-C ₆ H ₄	2c	4c	70
4	1a	H	4-Cl-C ₆ H ₄	2d	4d	68
5	1a	H	4-F-C ₆ H ₄	2e	4e	70
6	1a	H	4-Me-C ₆ H ₄	2f	4f	67
7	1a	H	4-Et-C ₆ H ₄	2g	4g	65
8	1a	H	1-Naphthyl	2h	4h	72
9	1a	H	Propyl	2i	4i	69
10	1a	H	Hexyl	2j	4j	65
11	1a	H	Isopropyl	2k	4k	65
12	1a	H	2-Naphthyl	2l	4l	75
13	1a	H	3,5-Me ₂ -C ₆ H ₃	2m	4m	64
14	1a	H	2-OMe-C ₆ H ₅	2n	4n	65
15	1a	H	4-Isopropyl-C ₆ H ₄	2o	4o	65
16	1b	Cl	C ₆ H ₅	2a	4p	72
17	1c	F	C ₆ H ₅	2a	4q	68
18	1d	Br	C ₆ H ₅	2a	4r	66

^a All the reactions were carried out on 3 mmol scale; ^b Isolated yields were based on the MBH adducts.

A plausible mechanism for the formation of the 2-methyl-3-(phenylthiomethyl)quinoline derivatives from the corresponding MBH adducts via reductive cyclization in the presence of Fe/AcOH is presented in Scheme 2.

Scheme 2. A Plausible mechanism for the formation of 2-methyl-3-(phenylthiomethyl)quinoline derivatives.

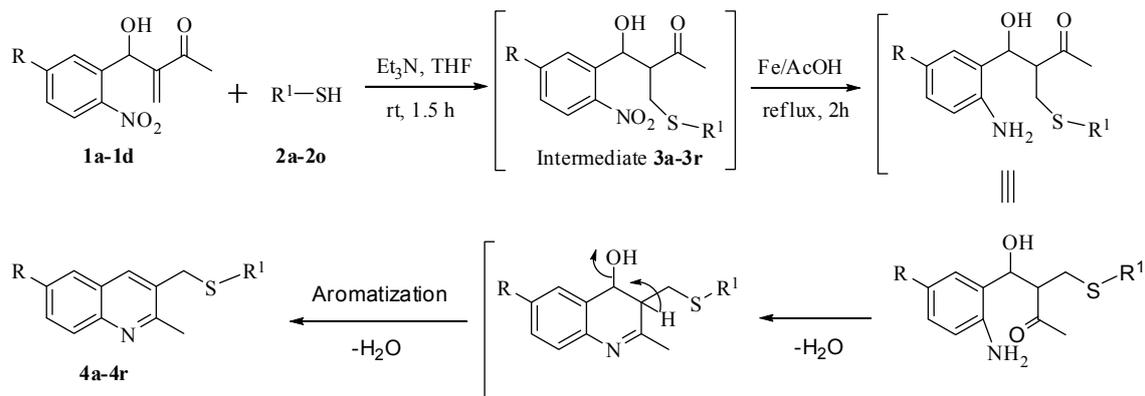
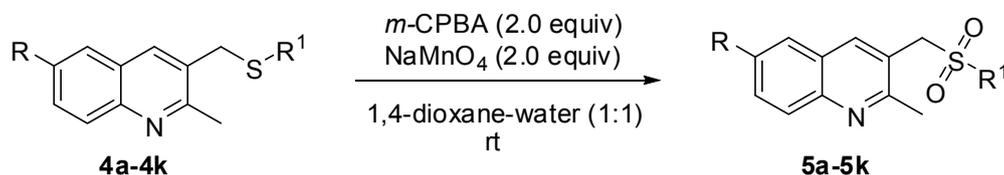


Table 2. Synthesis of 2-methyl-3-(phenylsulfonylmethyl)quinoline derivatives.



Entry	Substrate 4	R	R ¹	Time (min)	Product 5	Yield(%) ^{a,b}
1	4a	H	C ₆ H ₅	20	5a	85
2	4b	H	4-OMe-C ₆ H ₄	20	5b	89
3	4c	H	4-Br-C ₆ H ₄	40	5c	81
4	4d	H	4-Cl-C ₆ H ₄	40	5d	80
5	4e	H	4-F-C ₆ H ₄	35	5e	82
6	4f	H	4-Me-C ₆ H ₄	20	5f	87
7	4g	H	4-Et-C ₆ H ₄	20	5g	86
8	4h	H	1-Naphthyl	20	5h	87
9	4i	H	Propyl	20	5i	77
10	4j	H	Hexyl	20	5j	75
11	4k	H	Isopropyl	30	5k	78

^a All the reactions were carried out on 2 mmol scale; ^b Isolated yields.

Owing to the well known bioactivity of sulfones [33], the derived alkyl and arylthiomethylquinolines **4a–k** were oxidized to the corresponding sulfones **5a–k** in 75–89% yields (Table 2), following a reported procedure [34]. Here too, the substituents didn't have any significant effect on the yields of the products. As before, all these products were also fully characterized by ¹H- and ¹³C-NMR and by LR and HRMS data.

3. Experimental

3.1. General

All the reactions were performed in oven (130 °C) dried glassware under an inert atmosphere of nitrogen unless otherwise specified. Solvents for extraction and chromatography were distilled before

use. All the chemicals used in this study were of commercial grade and used after distillation. Analytical thin layer chromatography was performed with E. Merck silica gel 60 F254 aluminum plates. All purifications were carried out by flash chromatography using 230–400 mesh silica gel. ^1H and ^{13}C -NMR were recorded on a Bruker Avance EX 400 FT NMR (Taipei, Taiwan). Chemical shifts were reported in parts per million (δ) using TMS as internal standard and coupling constants were expressed in Hertz. Mass spectra were obtained on a JOEL SX-102A spectrometer (Taipei, Taiwan) at an ionization potential of 70 eV and data are reported as mass/charge (m/z) with the percent relative abundance. High-resolution mass spectra (HRMS) were acquired with a Finnigan MAT-95XL spectrometer (Taipei, Taiwan).

3.2. General Procedure for the Synthesis of Compounds **4a–r**

To a stirred solution of MBH adduct **1a** (3.0 mmol, 1 equiv) and benzenethiol **2a** (1.2 equiv) in THF (15 mL), triethylamine (1.5 equiv) was added dropwise, and the reaction mixture was allowed to continue at room temperature for 1.5 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was removed under reduced pressure. The residue was diluted with AcOH (15 mL) and Fe powder (6.0 equiv) at room temperature was added. Then the reaction mixture was heated at 110 °C for 2 h and was cooled to room temperature. AcOH was removed under reduced pressure and the residue was diluted with EtOAc (30 mL). The resulting mixture was filtered to remove any iron impurities. Iron residue was washed twice with EtOAc (30 mL). Filtrate and washings were combined and dried over anhydrous Na_2SO_4 . Solvent was evaporated and the residue, thus obtained was purified by column chromatography to provide the desired product **4a** as yellow solid in 66% isolated yield.

2-Methyl-3-(phenylthiomethyl)quinoline (4a). Yellow solid, m.p. 83–85 °C. ^1H -NMR ($\text{DMSO}-d_6$) δ 8.03 (s, 1H), 7.89 (d, $J = 8.3$ Hz, 1H), 7.78 (d, $J = 7.8$ Hz, 1H), 7.68–7.64 (m, 1H), 7.50–7.47 (m, 1H), 7.38–7.37 (m, 2H), 7.31–7.28 (m, 2H), 7.22–7.19 (m, 1H), 4.42 (s, 2H), 2.75 (s, 3H). ^{13}C -NMR (CDCl_3) δ 158.3, 147.1, 136.1, 135.4, 131.4, 129.4, 129.3, 129.2, 128.4, 127.4, 127.3, 127.0, 126.1, 37.6, 23.3. MS (m/z) (relative intensity): 265 (M^+ , 100), 156 (91). HRMS calcd. for $\text{C}_{17}\text{H}_{15}\text{NS}$ (M^+) 265.0920, found 265.0931.

3-((4-Methoxyphenylthio)methyl)-2-methyl quinoline (4b). Yellow solid, m.p. 65–67 °C. ^1H -NMR (CDCl_3) δ 7.98 (d, $J = 8.4$ Hz, 1H), 7.61–7.57 (m, 1H), 7.55 (d, $J = 8.1$ Hz, 1H), 7.47 (s, 1H), 7.40–7.36 (m, 1H), 7.18 (d, $J = 8.5$ Hz, 2H), 6.72 (d, $J = 8.5$ Hz, 2H), 4.02 (s, 2H), 3.69 (s, 3H), 2.76 (s, 3H). ^{13}C -NMR (CDCl_3) δ 159.7, 158.2, 146.8, 135.9, 135.2, 129.6, 129.1, 128.3, 127.1, 126.8, 125.8, 125.0, 114.5, 55.3, 39.3, 23.1. MS (m/z) (relative intensity): 295 (M^+ , 8), 157 (6), 156 (100), 149 (16). HRMS calcd. for $\text{C}_{18}\text{H}_{17}\text{NOS}$ (M^+) 295.1025, found 295.1032.

3-((4-Bromophenylthio)methyl)-2-methylquinoline (4c). Yellow solid, m.p. 118–120 °C. ^1H -NMR ($\text{DMSO}-d_6$) δ 8.05 (s, 1H), 7.89 (d, $J = 8.3$ Hz, 1H), 7.80 (d, $J = 8.0$ Hz, 1H), 7.69–7.65 (m, 1H), 7.51–7.46 (m, 3H), 7.32 (d, $J = 8.4$ Hz, 2H), 4.43 (s, 2H), 2.75 (s, 3H). ^{13}C -NMR (100 MHz, CDCl_3) δ 158.2, 147.2, 136.1, 134.6, 132.9, 132.3, 129.6, 128.8, 128.6, 127.4, 127.0, 126.2, 121.5, 37.7, 23.3. MS (m/z) (relative intensity): 345 ($\text{M}^+ + 2$, 6), 343 (M^+ , 6), 157 (20), 156 (100), 129 (8), 115 (11), 69

(11). HRMS calcd for $C_{17}H_{14}^{79}BrNS$ (M^+) 343.0025 found 343.0031; HRMS calcd. for $C_{17}H_{14}^{81}BrNS$ (M^+) 345.0004, found 345.0016.

3-((4-Chlorophenylthio)methyl)-2-methylquinoline (4d). Red solid, m.p. 98–100 °C. 1H -NMR (DMSO- d_6) δ 8.04 (s, 1H), 7.89 (d, $J = 8.4$ Hz, 1H), 7.80 (d, $J = 8.0$ Hz, 1H), 7.69–7.65 (m, 1H), 7.51–7.47 (m, 1H) 7.39 (d, $J = 8.6$ Hz, 2H), 7.35 (d, $J = 8.6$ Hz, 2H), 4.43 (s, 2H), 2.75 (s, 3H). ^{13}C -NMR (CDCl₃) δ 158.3, 147.2, 136.1, 133.8, 133.6, 132.9, 129.6, 129.3, 128.9, 128.5, 127.4, 127.0, 126.2, 38.0, 23.3. MS (m/z) (relative intensity): 299 (M^+ , 9), 157 (16), 156 (100), 129 (10), 115 (11). HRMS calcd for $C_{17}H_{14}^{35}ClNS$ (M^+) 299.0530 found 299.0540; HRMS calcd. for $C_{17}H_{14}^{37}ClNS$ (M^+) 301.0500, found 301.0515.

3-((4-Fluorophenylthio)methyl)-2-methylquinoline (4e). Yellow solid, m.p. 106–108 °C. 1H -NMR (DMSO- d_6) δ 7.92 (s, 1H), 7.88 (d, $J = 8.4$ Hz, 1H), 7.77 (d, $J = 8.0$ Hz, 1H), 7.68–7.64 (m, 1H), 7.50–7.46 (m, 1H), 7.42–7.39 (m, 2H), 7.15–7.11 (m, 2H), 4.37 (s, 2H), 2.74 (s, 3H). ^{13}C -NMR (CDCl₃) δ 162.6 (d, $J = 247.0$ Hz), 158.2, 147.1, 136.0, 134.8 (d, $J = 8.0$ Hz), 129.9 (d, $J = 3.0$ Hz), 129.4, 129.1, 128.5, 127.2, 126.9, 126.1, 116.2 (d, $J = 22.0$ Hz), 38.9, 23.2. MS (m/z) (relative intensity): 283 (M^+ , 20), 157 (22), 156 (100), 129 (15), 115(16). HRMS calcd. for $C_{17}H_{14}FNS$ (M^+) 283.0826, found 283.0832.

2-Methyl-3-(p-tolylthiomethyl)quinoline (4f). Yellow solid, m.p. 90–92 °C. 1H -NMR (CDCl₃) δ 7.99 (d, $J = 8.4$ Hz, 1H), 7.70 (s, 1H), 7.66–7.62 (m, 2H), 7.45–7.42 (m, 1H), 7.20 (d, $J = 7.8$ Hz, 2H), 7.05 (d, $J = 7.8$ Hz, 2H), 4.17 (s, 2H), 2.81 (s, 3H), 2.30 (s, 3H). ^{13}C -NMR (CDCl₃) δ 158.4, 147.1, 137.6, 136.0, 132.1, 131.5, 129.9, 129.5, 129.3, 128.5, 127.3, 127.0, 126.0, 38.3, 23.3, 21.2. MS (m/z) (relative intensity): 279 (M^+ , 13), 157 (10), 156 (100), 129 (8), 115 (7). HRMS calcd. for $C_{18}H_{17}NS$ (M^+) 279.1076, found 279.1083.

3-((4-Ethylphenylthio)methyl)-2-methylquinoline (4g). Brown liquid. 1H -NMR (CDCl₃) δ 8.00 (d, $J = 8.4$ Hz, 1H), 7.63 (s, 1H), 7.61–7.57 (m, 2H), 7.42–7.38 (m, 1H), 7.20 (d, $J = 8.1$ Hz, 2H), 7.05 (d, $J = 8.1$ Hz, 2H), 4.12 (s, 2H), 2.79 (s, 3H), 2.57 (q, $J = 7.6$ Hz, 2H), 1.18 (t, $J = 7.6$ Hz, 3H). ^{13}C -NMR (CDCl₃) δ 158.3, 147.0, 143.8, 135.9, 132.1, 131.7, 129.4, 129.2, 128.6, 128.3, 127.2, 126.9, 125.9, 38.1, 28.5, 23.2, 15.6. MS (m/z) (relative intensity): 293 (M^+ , 17), 157 (12), 156 (100), 149 (24), 129 (8). HRMS calcd. for $C_{19}H_{19}NS$ (M^+) 293.1233, found 293.1242.

2-Methyl-3-((naphthalen-1-ylthio)methyl)quinoline (4h). Yellow solid, m.p. 85–87 °C. 1H -NMR (CDCl₃) δ 8.44 (d, $J = 8.2$ Hz, 1H), 7.98 (d, $J = 8.4$ Hz, 1H), 7.85 (d, $J = 7.7$ Hz, 1H), 7.77 (d, $J = 8.2$ Hz, 1H), 7.64–7.60 (m, 1H), 7.55–7.48 (m, 3H), 7.44–7.37 (m, 3H), 7.29 (d, $J = 7.4$ Hz, 1H), 4.23 (s, 2H), 2.85 (s, 3H). ^{13}C -NMR (CDCl₃) δ 158.3, 147.1, 136.1, 134.1, 133.7, 132.2, 131.5, 129.3, 129.2, 128.8, 128.7, 128.4, 127.2, 127.0, 126.9, 126.4, 126.0, 125.6, 125.2, 37.8, 23.3. MS (m/z) (relative intensity): 315 (M^+ , 100), 156 (70). HRMS calcd. for $C_{21}H_{17}NS$ (M^+) 315.1076, found 315.1087.

2-Methyl-3-(propylthiomethyl)quinoline (4i). Yellow solid, m.p. 44–46 °C. 1H -NMR (CDCl₃) δ 8.00 (d, $J = 8.4$ Hz, 1H), 7.90 (s, 1H), 7.74 (d, $J = 8.0$ Hz, 1H), 7.66–7.63 (m, 1H), 7.49–7.45 (m, 1H), 3.84 (s, 2H), 2.81 (s, 3H), 2.45 (t, $J = 7.2$ Hz, 2H), 1.66–1.57(m, 2H), 0.97 (t, $J = 7.3$ Hz, 3H). ^{13}C -NMR

(CDCl₃) δ 158.6, 147.0, 135.6, 130.1, 129.2, 128.5, 127.2, 127.0, 126.1, 34.2, 34.0, 23.2, 22.7, 13.6. MS (m/z) (relative intensity): 231 (M^+ , 100), 156 (51). HRMS calcd. for C₁₄H₁₇NS (M^+) 231.1076, found 231.1086.

3-(Hexylthiomethyl)-2-methylquinoline (4j). Yellow liquid. ¹H-NMR (CDCl₃) δ 8.00 (d, J = 8.4 Hz, 1H), 7.89 (s, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.66–7.62 (m, 1H), 7.49–7.45 (m, 1H), 3.84 (s, 2H), 2.81 (s, 3H), 2.46 (t, J = 7.4 Hz, 2H), 1.60–1.54 (m, 2H), 1.37–1.22 (m, 6H), 0.86 (t, J = 6.7 Hz, 3H). ¹³C-NMR (CDCl₃) δ 158.4, 146.8, 135.3, 129.9, 129.0, 128.3, 127.0, 126.8, 125.8, 34.1, 31.8, 31.3, 29.1, 28.5, 23.0, 22.4, 13.9. MS (m/z) (relative intensity): 273 (M^+ , 100), 189 (7), 156 (62). HRMS calcd. for C₁₇H₂₃NS (M^+) 273.1546, found 273.1554.

3-(Isopropylthiomethyl)-2-methylquinoline (4k). Yellow liquid. ¹H-NMR (DMSO-*d*₆) δ 8.13 (s, 1H), 7.91–7.88 (m, 2H), 7.69–7.65 (m, 1H), 7.53–7.50 (m, 1H), 3.95 (s, 2H), 2.88–2.81 (m, 1H), 2.73 (s, 3H), 1.24 (d, J = 6.8 Hz, 6H). ¹³C-NMR (CDCl₃) δ 158.4, 146.7, 135.4, 130.1, 129.0, 128.2, 127.0, 126.9, 125.9, 34.9, 32.7, 23.1, 22.9. MS (m/z) (relative intensity): 231 (M^+ , 100), 156 (46). HRMS calcd. for C₁₄H₁₇NS (M^+) 231.1076, found 231.1086.

2-Methyl-3-((naphthalen-2-ylthio)methyl)quinoline (4l). Yellow solid, m.p. 115–117 °C. ¹H-NMR (CDCl₃) δ 8.00 (d, J = 8.4 Hz, 1H), 7.79–7.77 (m, 2H), 7.75–7.73 (m, 2H), 7.68–7.57 (m, 3H), 7.47–7.39 (m, 4H), 4.33 (s, 2H), 2.86 (s, 3H). ¹³C-NMR (CDCl₃) δ 158.3, 147.1, 136.1, 133.8, 133.0, 132.3, 129.4, 129.3, 129.1, 128.7, 128.5, 128.4, 127.8, 127.4, 127.3, 127.0, 126.7, 126.2, 126.0, 37.4, 23.3. MS (m/z) (relative intensity): 315 (M^+ , 21), 157 (12), 156 (100), 129 (8), 115 (18). HRMS calcd. for C₂₁H₁₇NS (M^+) 315.1076, found 315.1083.

3-((3,5-Dimethylphenylthio)methyl)-2-methylquinoline (4m). Yellow solid, m.p. 108–110 °C. ¹H-NMR (CDCl₃) δ 8.00 (d, J = 8.7 Hz, 1H), 7.75 (s, 1H), 7.66–7.62 (m, 2H), 7.46–7.42 (m, 1H), 6.92 (s, 2H), 6.85 (s, 1H), 4.20 (s, 2H), 2.83 (s, 3H), 2.22 (s, 6H). ¹³C-NMR (DMSO-*d*₆) δ 158.1, 146.3, 138.1, 135.6, 134.7, 129.2, 129.1, 128.0, 127.8, 127.2, 126.9, 126.4, 125.8, 35.0, 22.7, 20.6. MS (m/z) (relative intensity): 293 (M^+ , 32), 157 (11), 156 (100), 151 (15). HRMS calcd. for C₁₉H₁₉NS (M^+) 293.1233, found 293.1241.

3-((2-Methoxyphenylthio)methyl)-2-methylquinoline (4n). Yellow solid, m.p. 118–120 °C. ¹H-NMR (CDCl₃) δ 7.98 (d, J = 8.3 Hz, 1H), 7.71 (s, 1H), 7.63–7.59 (m, 2H), 7.43–7.39 (m, 1H), 7.23–7.19 (m, 2H), 6.84–6.80 (m, 2H), 4.18 (s, 2H), 3.81 (s, 3H), 2.84 (s, 3H). ¹³C-NMR (CDCl₃) δ 158.7, 158.6, 147.1, 136.0, 132.9, 129.5, 129.2, 129.0, 128.4, 127.3, 127.1, 125.9, 123.0, 121.2, 110.8, 55.9, 35.8, 23.2. MS (m/z) (relative intensity): 295 (M^+ , 12), 157 (7), 156 (100). HRMS calcd. for C₁₈H₁₇NOS (M^+) 295.1025, found 295.1034.

3-((4-Isopropylphenylthio)methyl)-2-methylquinoline (4o). Red solid, m.p. 44–46 °C. ¹H-NMR (DMSO-*d*₆) δ 7.96 (s, 1H), 7.89 (d, J = 8.4 Hz, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.68–7.64 (m, 1H), 7.50–7.46 (m, 1H), 7.28 (d, J = 8.0 Hz, 2H), 7.16 (d, J = 8.1 Hz, 2H), 4.36 (s, 2H), 2.86–2.79 (m, 1H), 2.74 (s, 3H), 1.14 (d, J = 6.8 Hz, 6H). ¹³C-NMR (DMSO-*d*₆) δ 158.1, 147.1, 146.2, 135.4, 131.8, 130.2, 129.3,

129.1, 127.8, 127.2, 127.0, 126.4, 125.8, 35.8, 32.9, 23.6, 22.7. MS (m/z) (relative intensity): 307 (M^+ , 65), 156 (100). HRMS calcd. for $C_{20}H_{21}NS$ (M^+) 307.1389, found 307.1403.

6-Chloro-2-methyl-3-(phenylthiomethyl)quinoline (4p). Green solid, m.p. 74–76 °C. 1H -NMR (DMSO- d_6) δ 8.00 (s, 1H), 7.91–7.88 (m, 2H), 7.65 (d, $J = 8.9$ Hz, 1H), 7.37–7.35 (m, 2H), 7.31–7.27 (m, 2H), 7.22–7.19 (m, 1H), 4.40 (s, 2H), 2.74 (s, 3H). ^{13}C -NMR ($CDCl_3$) δ 158.7, 145.5, 135.1, 135.0, 131.8, 131.7, 130.4, 130.3, 130.2, 129.2, 127.7, 127.5, 125.9, 37.7, 23.3. MS (m/z) (relative intensity): 299 (M^+ , 10), 192 (23), 190 (100), 155 (10). HRMS calcd. for $C_{17}H_{14}^{35}CINS$ (M^+) 299.0530, found 299.0540; HRMS calcd. for $C_{17}H_{14}^{37}CINS$ (M^+) 301.0500, found 301.0515.

6-Fluoro-2-methyl-3-(phenylthiomethyl)quinoline (4q). Yellow solid, m.p. 44–46 °C. 1H -NMR (DMSO- d_6) δ 8.02 (s, 1H), 7.95 (dd, $J = 9.0, 5.4$ Hz, 1H), 7.62–7.53 (m, 2H), 7.37–7.35 (m, 2H), 7.31–7.27 (m, 2H), 7.23–7.19 (m, 1H), 4.40 (s, 2H), 2.73 (s, 3H). ^{13}C -NMR (DMSO- d_6) δ 159.3 (d, $J = 242.0$ Hz), 157.6, 143.4, 135.0, 134.9 (d, $J = 5.0$ Hz), 130.6 (d, $J = 9.0$ Hz), 130.2, 129.5, 129.0, 127.0 (d, $J = 10.0$ Hz), 126.5, 118.9 (d, $J = 25.0$ Hz), 110.3 (d, $J = 21.0$ Hz), 35.0, 22.6. MS (m/z) (relative intensity): 283 (M^+ , 15), 175 (7), 174 (100), 147 (6). HRMS calcd. for $C_{17}H_{14}FNS$ (M^+) 283.0826, found 283.0830.

6-Bromo-2-methyl-3-(phenylthiomethyl)quinoline (4r). Yellow solid, m.p. 78–80 °C. 1H -NMR (DMSO- d_6) δ 8.08 (d, $J = 1.9$ Hz, 1H), 8.01 (s, 1H), 7.83 (d, $J = 8.9$ Hz, 1H), 7.77 (dd, $J = 8.9, 1.8$ Hz, 1H), 7.37–7.35 (m, 2H), 7.31–7.28 (m, 2H), 7.23–7.19 (m, 1H), 4.41 (s, 2H), 2.74 (s, 3H). ^{13}C -NMR (DMSO- d_6) δ 158.9, 144.8, 134.8, 134.5, 132.1, 130.4, 130.0, 129.6, 129.1, 129.0, 127.7, 126.5, 118.6, 35.0, 22.7. MS (m/z) (relative intensity): 345 ($M^+ + 2$, 9), 343 (M^+ , 8), 236 (97), 234 (100), 156 (24), 155 (36), 149 (18), 114 (19). HRMS calcd. for $C_{17}H_{14}^{79}BrNS$ (M^+) 343.0025, found 343.0024. HRMS calcd. for $C_{17}H_{14}^{81}BrNS$ (M^+) 345.004, found 345.0015.

3.3. General Procedure for the Synthesis of Compounds 5a–k

To a stirred solution of sulfide **4a** (2.0 mmol, 1 equiv) in 1:1 1,4-dioxane/ H_2O (12 mL) was added *m*-CPBA (2.0 equiv.) followed by sodium permanganate (2.0 equiv.) at room temperature (25 °C), and the reaction mixture was stirred at same temperature for 20 min. After completion of the reaction as monitored by TLC, the reaction mixture was extracted with EtOAc (30 mL), then organic layer was washed with saturated $NaHCO_3$, water, followed by brine solution and dried over Na_2SO_4 . Solvent was evaporated and obtained crude product was purified by column chromatography to provide the desired sulfone **5a** as yellow solid in 85 % isolated yield.

2-Methyl-3-(phenylsulfonylmethyl)quinoline (5a). Yellow solid, m.p. 148–150 °C. 1H -NMR ($CDCl_3$) δ 7.99 (d, $J = 8.4$ Hz, 1H), 7.89 (s, 1H), 7.73–7.63 (m, 5H), 7.52–7.46 (m, 3H), 4.53 (s, 2H), 2.48 (s, 3H). ^{13}C -NMR ($CDCl_3$) δ 158.3, 147.3, 139.6, 138.2, 134.3, 130.4, 129.4, 128.7, 128.6, 127.6, 126.6, 126.5, 120.8, 59.7, 23.2. MS (m/z) (relative intensity): 297 (M^+ , 3), 157 (31), 156 (100), 129 (16), 115 (19). HRMS calcd. for $C_{17}H_{15}NO_2S$ (M^+) 297.0818, found 297.0830.

3-((4-Methoxyphenylsulfonyl)methyl)-2-methylquinoline (5b). White solid, m.p. 178–180 °C. 1H -NMR (DMSO- d_6) δ 7.99 (s, 1H), 7.91 (d, $J = 8.3$ Hz, 1H), 7.84 (d, $J = 8.0$ Hz, 1H), 7.74–7.71 (m, 1H), 7.65

(d, $J = 8.7$ Hz, 2H), 7.56–7.52 (m, 1H), 7.12 (d, $J = 8.7$ Hz, 2H), 4.85 (s, 2H), 3.84 (s, 3H), 2.54 (s, 3H). $^{13}\text{C-NMR}$ (CDCl_3) δ 164.2, 158.4, 147.6, 139.6, 130.9, 130.4, 129.6, 128.6, 127.7, 126.7, 126.4, 121.3, 114.6, 59.8, 55.8, 23.3. MS (m/z) (relative intensity): 327 (M^+ , 27), 157 (89), 156 (100), 129 (30), 128 (12), 116 (20), 115 (63), 89 (13). HRMS calcd. for $\text{C}_{18}\text{H}_{17}\text{NO}_3\text{S}$ (M^+) 327.0924, found 327.0936.

3-((4-Bromophenylsulfonyl)methyl)-2-methylquinoline (**5c**). White solid, m.p. 213–215 °C. $^1\text{H-NMR}$ (CDCl_3) δ 8.00 (d, $J = 8.6$ Hz, 1H), 7.91 (s, 1H), 7.74–7.71 (m, 2H), 7.62 (d, $J = 8.4$ Hz, 2H), 7.53–7.51 (m, 3H), 4.52 (s, 2H), 2.51 (s, 3H). $^{13}\text{C-NMR}$ (CDCl_3) δ 158.2, 147.8, 139.7, 137.2, 132.8, 130.6, 130.3, 129.8, 128.7, 127.6, 126.7, 126.6, 120.5, 59.7, 23.4. MS (m/z) (relative intensity): 376 ($\text{M}^+ + 2$, 3), 374 (M^+ , 3), 157 (89), 156 (100), 154 (11), 129 (30), 115 (62), 89 (13). HRMS calcd. for $\text{C}_{17}\text{H}_{14}^{79}\text{BrNO}_2\text{S}$ (M^+) 374.9923, found 374.9937; HRMS calcd. for $\text{C}_{17}\text{H}_{14}^{81}\text{BrNO}_2\text{S}$ (M^+) 376.9903, found 376.9922.

3-((4-Chlorophenylsulfonyl)methyl)-2-methyl quinoline (**5d**). White solid, m.p. 190–192 °C. $^1\text{H-NMR}$ (CDCl_3) δ 7.99 (d, $J = 8.7$ Hz, 1H), 7.91 (s, 1H), 7.74–7.71 (m, 2H), 7.59 (d, $J = 8.5$ Hz, 2H), 7.53–7.50 (m, 1H), 7.44 (d, $J = 8.5$ Hz, 2H), 4.53 (s, 2H), 2.50 (s, 3H). $^{13}\text{C-NMR}$ (CDCl_3) δ 158.2, 147.8, 141.2, 139.7, 136.6, 130.6, 130.2, 129.8, 128.7, 127.6, 126.7, 126.6, 120.5, 59.7, 23.4. HRMS calcd. for $\text{C}_{17}\text{H}_{14}\text{ClNO}_2\text{S}$ (M^+) 331.0434, found 331.0437.

3-((4-Fluorophenylsulfonyl)methyl)-2-methyl quinoline (**5e**). White solid, m.p. 183–185 °C. $^1\text{H-NMR}$ (CDCl_3) δ 7.99 (d, $J = 8.5$ Hz, 1H), 7.89 (s, 1H), 7.74–7.65 (m, 4H), 7.53–7.49 (m, 1H), 7.16–7.12 (m, 2H), 4.53 (s, 2H), 2.51 (s, 3H). $^{13}\text{C-NMR}$ ($\text{DMSO-}d_6$) δ 165.2 (d, $J = 252.0$ Hz), 158.7, 146.7, 139.4, 134.7 (d, $J = 2.0$ Hz), 131.4 (d, $J = 10.0$ Hz), 130.0, 127.9, 127.5, 126.1, 126.0, 121.2, 116.5 (d, $J = 23.0$ Hz), 58.0, 22.9. HRMS calcd. for $\text{C}_{17}\text{H}_{14}\text{FNO}_2\text{S}$ (M^+) 315.0729, found 315.0732.

2-Methyl-3-(tosylmethyl)quinoline (**5f**). Yellow solid, m.p. 180–182 °C. $^1\text{H-NMR}$ ($\text{DMSO-}d_6$) δ 8.01 (s, 1H), 7.91 (d, $J = 8.4$ Hz, 1H), 7.84 (d, $J = 8.0$ Hz, 1H), 7.75–7.71 (m, 1H), 7.63 (d, $J = 8.0$ Hz, 2H), 7.56–7.52 (m, 1H), 7.42 (d, $J = 8.0$ Hz, 2H), 4.88 (s, 2H), 2.52 (s, 3H), 2.40 (s, 3H). $^{13}\text{C-NMR}$ (CDCl_3) δ 158.3, 147.7, 145.4, 139.6, 135.2, 130.4, 130.0, 128.7, 128.6, 127.6, 126.7, 126.4, 121.0, 59.7, 23.3, 21.7. HRMS calcd. for $\text{C}_{18}\text{H}_{17}\text{NO}_2\text{S}$ (M^+) 311.0980, found 311.0985.

3-((4-Ethylphenylsulfonyl)methyl)-2-methyl quinoline (**5g**). White solid, m.p. 160–162 °C. $^1\text{H-NMR}$ ($\text{DMSO-}d_6$) δ 7.97 (s, 1H), 7.91 (d, $J = 8.3$ Hz, 1H), 7.82 (d, $J = 8.0$ Hz, 1H), 7.75–7.71 (m, 1H), 7.66 (d, $J = 7.8$ Hz, 2H), 7.55–7.52 (m, 1H), 7.45 (d, $J = 7.8$ Hz, 2H), 4.88 (s, 2H), 2.70 (q, $J = 7.5$ Hz, 2H), 2.54 (s, 3H), 1.19 (t, $J = 7.5$ Hz, 3H). $^{13}\text{C-NMR}$ (CDCl_3) δ 158.4, 151.5, 147.6, 139.6, 135.3, 130.4, 128.9, 128.8, 128.5, 127.6, 126.6, 126.4, 121.0, 59.7, 29.0, 23.2, 15.2. HRMS calcd. for $\text{C}_{19}\text{H}_{19}\text{NO}_2\text{S}$ (M^+) 325.1136, found 325.1125.

2-Methyl-3-((naphthalen-1-ylsulfonyl)methyl) quinoline (**5h**). White solid, m.p. 158–160 °C. $^1\text{H-NMR}$ (CDCl_3) δ 8.80–8.77 (m, 1H), 8.12 (d, $J = 8.2$ Hz, 1H), 8.02–7.93 (m, 3H), 7.69–7.61 (m, 4H), 7.55–7.53 (m, 1H), 7.46–7.42 (m, 2H), 4.70 (s, 2H), 2.51 (s, 3H). $^{13}\text{C-NMR}$ (CDCl_3) δ 158.4, 147.6,

139.6, 135.8, 134.2, 133.2, 131.7, 130.4, 129.5, 129.3, 129.0, 128.5, 127.5, 127.3, 126.5, 126.4, 124.5, 124.0, 120.9, 59.3, 23.4. HRMS calcd. for $C_{21}H_{17}NO_2S$ (M^+) 347.0980, found 347.0976.

2-Methyl-3-(propylsulfonylmethyl)quinoline (5i). White solid, m.p. 148–150 °C. 1H -NMR ($CDCl_3$) δ 8.15 (s, 1H), 8.02 (d, $J = 8.4$ Hz, 1H), 7.79 (d, $J = 8.1$ Hz, 1H), 7.73–7.69 (m, 1H), 7.53–7.49 (m, 1H), 4.42 (s, 2H), 3.00–2.96 (m, 2H), 2.86 (s, 3H), 1.96–1.88 (m, 2H), 1.08 (t, $J = 7.4$ Hz, 3H). ^{13}C -NMR ($CDCl_3$) δ 158.4, 147.9, 139.4, 130.5, 128.7, 127.7, 126.8, 126.6, 120.3, 56.2, 54.3, 23.9, 15.8, 13.3. HRMS calcd. for $C_{14}H_{17}NO_2S$ (M^+) 263.0980, found 263.0986.

3-(Hexylsulfonylmethyl)-2-methylquinoline (5j). White solid, m.p. 127–129 °C. 1H -NMR ($CDCl_3$) δ 8.15 (s, 1H), 8.02 (d, $J = 8.4$ Hz, 1H), 7.79 (d, $J = 8.0$ Hz, 1H), 7.73–7.69 (m, 1H), 7.53–7.49 (m, 1H), 4.42 (s, 2H), 3.01–2.97 (m, 2H), 2.86 (s, 3H), 1.91–1.84 (m, 2H), 1.46–1.39 (m, 2H), 1.33–1.25 (m, 4H), 0.86 (t, $J = 6.8$ Hz, 3H). ^{13}C -NMR ($CDCl_3$) δ 158.4, 147.9, 139.4, 130.5, 128.7, 127.7, 126.8, 126.6, 120.3, 56.1, 52.7, 31.3, 28.3, 24.0, 22.4, 22.0, 14.0. HRMS calcd. for $C_{17}H_{23}NO_2S$ (M^+) 305.1449, found 305.1460.

3-(Isopropylsulfonylmethyl)-2-methylquinoline (5k). White solid, m.p. 145–147 °C. 1H -NMR ($CDCl_3$) δ 8.15 (s, 1H), 8.10 (d, $J = 8.4$ Hz, 1H), 7.78 (d, $J = 8.1$ Hz, 1H), 7.72–7.68 (m, 1H), 7.50 (s, 1H), 4.39 (s, 2H), 3.25–3.18 (m, 1H), 2.85 (s, 3H), 1.14 (d, $J = 6.8$ Hz, 6H). ^{13}C -NMR ($CDCl_3$) δ 158.7, 147.7, 139.6, 130.3, 128.6, 127.6, 126.7, 126.4, 119.8, 53.5, 52.1, 23.8, 15.7. HRMS calcd. for $C_{14}H_{17}NO_2S$ (M^+) 263.0980, found 263.0988.

Crystallographic description of 3h: crystal size = $0.44 \times 0.32 \times 0.08$ mm³; $C_{21}H_{19}NO_4S$; $M_r = 381.43$; Monoclinic; Space group P 2₁/c; $a = 32.290(4)$ Å, $\alpha = 90^\circ$, $b = 7.4466(9)$ Å, $\beta = 103.742(6)^\circ$, $c = 15.7324(16)$ Å, $\gamma = 90^\circ$, $V = 3674.6(7)$ Å³; $Z = 8$; $\rho_{cal} = 1.379$ mg/m³; $\mu = 0.204$ mm⁻¹; $F(000) = 1600$; Theta range for data collection = 1.30 to 25.02°; Index ranges = $-29 \leq h \leq 38$, $-7 \leq k \leq 8$, $-16 \leq l \leq 18$; Reflections collected / Independent reflection = 13232/6139 [$R(int) = 0.0734$]; Completeness to theta = 25.02° 94.4%; Absorption correction = multi-scan; Max. and min. transmission = 0.9839 and 0.9158; Refinement method = Full-matrix least-squares on F²; Data / restraints / parameters = 6139/0/277; Goodness-of-fit on F² = 1.183; Final R indices = [$I > 2\sigma(I)$] $R1 = 0.2457$, $wR2 = 0.4913$; R indices (all data) = $R1 = 0.2811$, $wR2 = 0.5062$; Largest diff. peak and hole = 1.222 and -0.713 e.Å⁻³.

4. Conclusions

In conclusion, we have successfully synthesized 2-methyl-3-(phenylthiomethyl)quinoline derivatives in good yields from MBH adducts via a convenient one-pot procedure. The 2-methyl-3-(phenylthiomethyl)quinoline reaction products were transformed into the corresponding 2-methyl-3-(phenylsulfonylmethyl)quinoline derivatives in good yields. The C3-alkylthiomethylquinolines are very useful precursors for the synthesis of C3-alkylsulfonyl or C3-alkylsulfinyl containing quinoline derivatives.

Supplementary Materials

Supplementary materials can be accessed at: <http://www.mdpi.com/1420-3049/17/5/5081/s1>.

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Sample Availability: Samples of all compounds are available from the authors.

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