

Synthesis of novel 3-arylcyclopenta[*c*]quinolines via acid-induced domino cyclization of 2-arylamino-2-methylthioethenyl 2-arylcyclopropyl ketones

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Dedicated to Professor Lutz F. Tietze on his 65th birthday

Abstract

A novel acid-induced domino cyclization of *N,S*-anilinoacetals of type **3** derived from 2-arylcyclopropyl ketones, is reported which yields a wide range of substituted- and fused- 3-arylcyclopenta[*c*]quinolines **6** with concomitant formation of a cyclopentane and a quinoline ring.

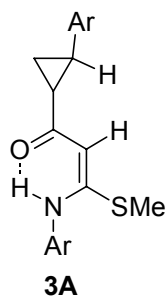
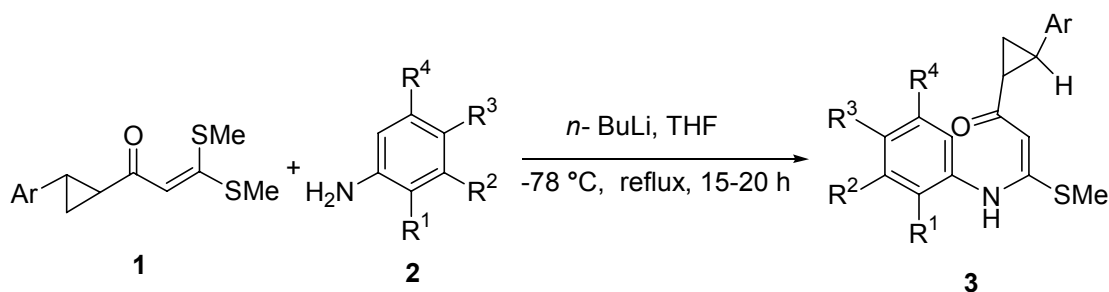
Keywords: Domino cyclization, cyclopenta[*c*]quinolines, *N,S*-anilinoacetals

Introduction

Substituted quinolines and their benzo- or hetero- fused analogues represent an important class of heterocyclic compounds because of their presence in numerous biologically active natural products, along with the wide spectrum of physiological activities displayed by these class of compounds.^{1,2} As a consequence, much attention has been focused towards developing new synthetic methods for substituted- and fused quinolines.^{1,3} Domino reactions are of growing interest in synthetic organic chemistry because they allow rapid construction of polycyclic structures in a single operation and confer great strategic value in molecular construction.⁴ Our own interest in this regard has been concerned with the elaboration of domino reactions involving acid-induced rearrangements of 2-aryl-(or heteroaryl)-cyclopropyl ketones with an α -(bismethylthio)-methylene functionality as the cationic cyclization terminator, which yield a range of carbocyclic products such as substituted cyclopentanones,^{5a,b} cyclopenta[*b*]indanes,^{5c-d} diquinanes,^{5d} 1-aryllindanes,^{5e} bicyclo[3.2.1]octene,^{5f} and other cyclopentano-fused heterocycles.^{5g-i} In continuation of these studies, we now report the domino carbocationic cyclization of arylcyclopropyl ketones of type **3** carrying an (*N,S*-aminomethylene) functionality, yielding 3- arylcyclopenta[*c*]quinolines (compound **6**) in a single one-pot operation.

Results and Discussion

The cyclopropyl ketone (compound **1**) was prepared in quantitative yield by treatment with dimethyloxosulphonium methylide generated from the corresponding sulphonium salt to the corresponding unsaturated ketene *S,S*-acetals in the presence of phase transfer catalyst.^{5a,5i,6} The *N,S*-arylaminoacetals (compounds **3a–j**) required for studying this transformation were prepared by displacement of one of the methylthio groups of the corresponding α -oxoketene dithioacetals (compound **1**) by a substituted aniline in the presence of *n*-BuLi in THF.⁷ The structures of all these newly synthesized *N,S*-acetals (compounds **3a–j**) were confirmed with the help of spectral and analytical data. The ¹H NMR spectra of these *N,S*-acetals show that they exist in the intramolecular H-bonded form **3A**.

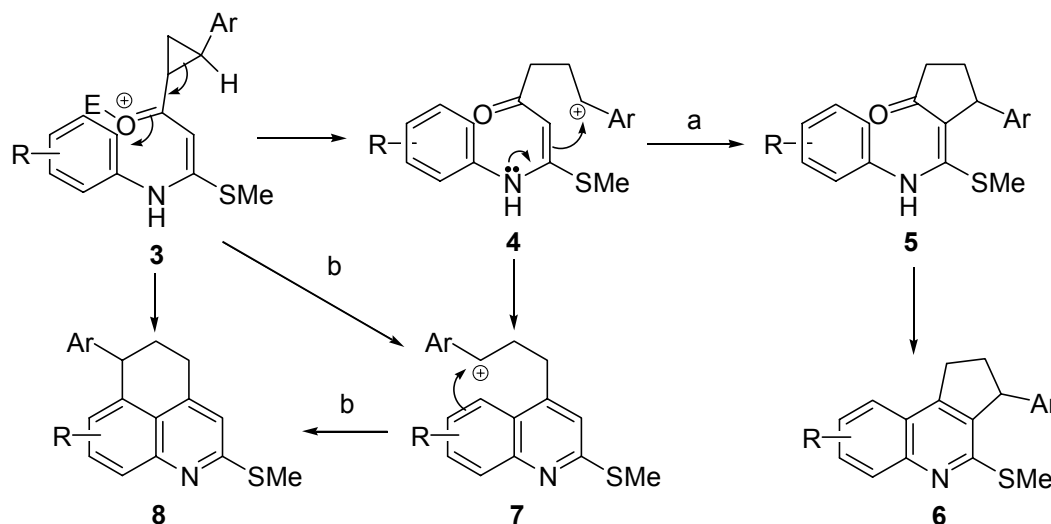


| Entry | 3 | Ar | R ¹ | R ² | R ³ | R ⁴ | % Yield |
|-------|-----------|---|----------------|----------------|----------------|----------------|---------|
| 1 | 3a | 4- MeOC ₆ H ₄ | H | MeO | MeO | H | 70 |
| 2 | 3b | 4- MeOC ₆ H ₄ | H | MeO | H | H | 71 |
| 3 | 3c | C ₆ H ₅ | H | MeO | H | H | 84 |
| 4 | 3d | 2,5- (MeO) ₂ C ₆ H ₃ | H | MeO | H | H | 73 |
| 5 | 3e | C ₆ H ₅ | MeO | H | H | MeO | 81 |
| 6 | 3f | 3,4- (MeO) ₂ C ₆ H ₃ | MeO | H | H | MeO | 79 |
| 7 | 3g | 4- MeOC ₆ H ₄ | H | H | MeO | H | 70 |
| 8 | 3h | 4- MeOC ₆ H ₄ | H | H | H | H | 76 |
| 9 | 3i | 4- MeOC ₆ H ₄ | H | Me | H | H | 88 |
| 10 | 3j | C ₆ H ₅ | H | Cl | H | H | 72 |

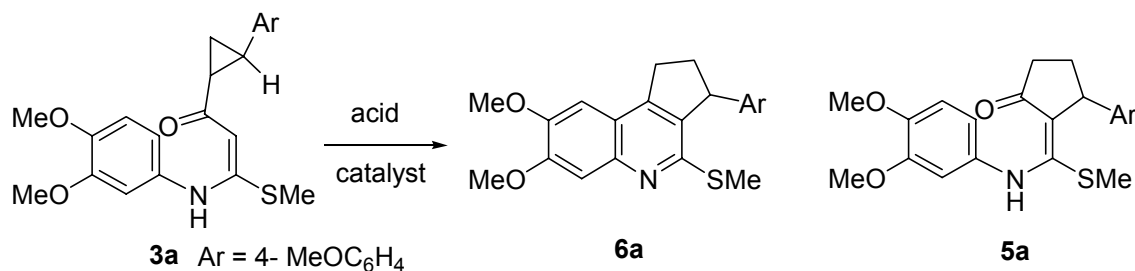
Scheme 1

The cyclization of the *N,S*-anilinoacetal (compound **3a**), bearing two strongly activating methoxy groups, was first examined in the presence of various protic and Lewis acids. It was envisaged that the initial acid-assisted ring-opening of the cyclopropyl ketone (compound **3**) would furnish the stable benzylic carbocation **4** which could be intercepted by the electron-rich *N,S*-anilino(methylene) double bond *via* a 5-*exo* process followed by intramolecular cyclocondensation of the resulting cyclopentanone *N,S*-acetal **5** to afford angularly-fused cyclopenta[*c*]quinolines (compound **6**) (Scheme 2, pathway a). Alternatively, the cyclopropyl

ketone (compound **3**) might undergo either stepwise or concomitant ring-opening and intramolecular cyclocondensation to give the quinoline **7** with a pendant α -arylpropyl carbocation side chain which can be captured intramolecularly by the electron-rich 5-position of quinoline to give novel *peri*-fused quinoline (compound **8**) (pathway b), as was observed in our previous studies.^{5g} However, a detailed study of the cyclization of compound **3a** under the influence of various Lewis and protic acids (H₃PO₄, TFA, PPA, CF₃SO₃H, SnCl₄, BF₃·OEt₂, Cu(OTf)₂, TiCl₄) revealed the formation of either the cyclopenta[*c*]quinoline (compound **6a**) or the cyclopentanone *N,S*-acetal **5a** as exclusive products in varying yields (Table 1), thus showing that cyclization *via* pathway 'a' is preferred over 'b'.



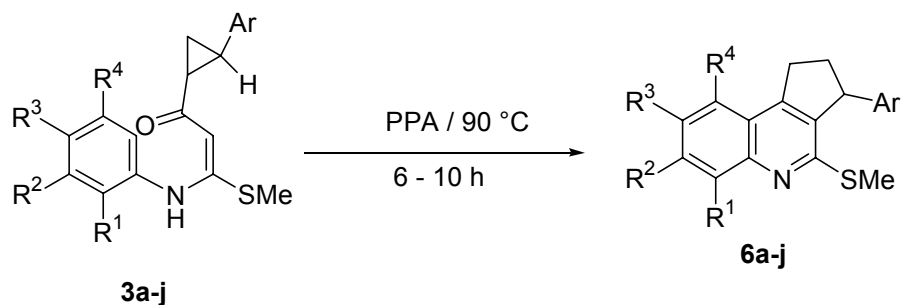
Scheme 2



The cyclization of compound **3a** was found to be most efficient in the presence of polyphosphoric acid at 90 °C; therefore all the subsequent cyclizations were carried out in the presence of this acid. Thus, Scheme 3 shows cyclization–rearrangement of the various substituted *N,S*-anilinoacetals (compounds **3a–j**) in the presence of PPA yielding the respective substituted 3-aryl-cyclopenta[*c*]quinolines (compounds **6a–j**) in 46–56% overall yields, which we were not able to improve.

Table 1. Lewis/protic acid-induced rearrangement of the cyclopropyl ketone (**3a**)

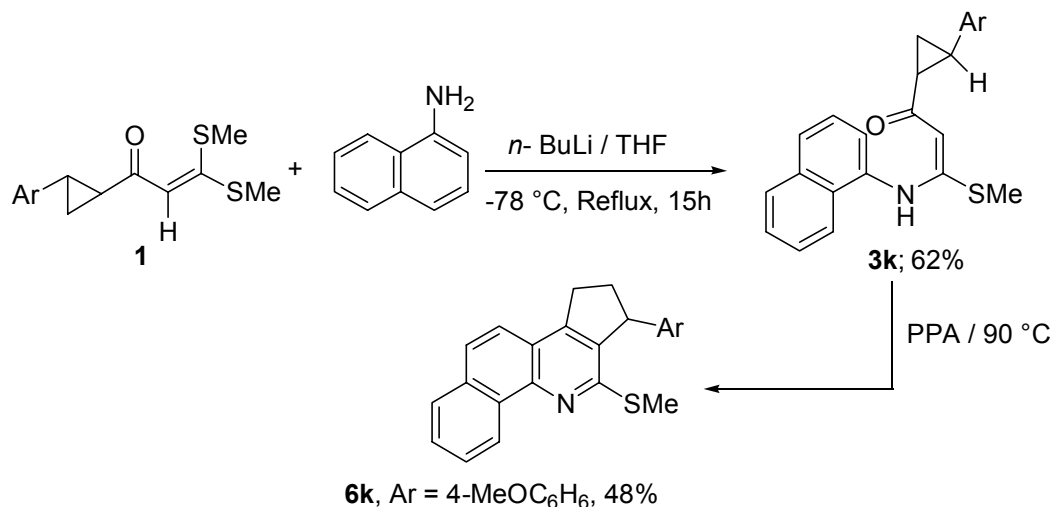
| Entry | 3 | Reaction Conditions | Time (h) | Products | |
|-------|-----------|---|----------|---------------------|---------------------|
| | | | | 6a (% Yield) | 5a (% Yield) |
| 1 | 3a | H ₃ PO ₄ / 60 °C / Δ | 4 | 34 | - |
| 2 | 3a | PPA / 90 °C / Δ | 8 | 53 | - |
| 3 | 3a | (CF ₃ SO ₃) ₂ Cu / CH ₂ Cl ₂ / RT | 4 | 30 | - |
| 4 | 3a | TFA / CH ₂ Cl ₂ / Δ | 20 | 24 | 18 |
| 5 | 3a | CF ₃ SO ₃ H, RT | 10 | 36 | 16 |
| 6 | 3a | SnCl ₄ / CH ₂ Cl ₂ / 0 °C - RT | 10 | - | 20 |
| 7 | 3a | SnCl ₄ / C ₆ H ₆ / reflux | 6 | 18 | 26 |
| 8 | 3a | BF ₃ .OEt ₂ / CH ₂ Cl ₂ / 0 °C - RT | 15 | - | 30 |
| 9 | 3a | BF ₃ .OEt ₂ / C ₆ H ₆ / reflux | 8 | 35 | - |
| 10 | 3a | TiCl ₄ / CH ₂ Cl ₂ / 0 °C - RT | 10 | - | 30 |



| Entry | 6 | Ar | R ¹ | R ² | R ³ | R ⁴ | % Yield |
|-------|-----------|---|----------------|----------------|----------------|----------------|---------|
| 1 | 6a | 4- MeOC ₆ H ₄ | H | MeO | MeO | H | 54 |
| 2 | 6b | 4- MeOC ₆ H ₄ | H | MeO | H | H | 56 |
| 3 | 6c | C ₆ H ₅ | H | MeO | H | H | 55 |
| 4 | 6d | 2,5- (MeO) ₂ C ₆ H ₃ | H | MeO | H | H | 54 |
| 5 | 6e | C ₆ H ₅ | MeO | H | H | MeO | 51 |
| 6 | 6f | 3,4- (MeO) ₂ C ₆ H ₃ | MeO | H | H | MeO | 54 |
| 7 | 6g | 4- MeOC ₆ H ₄ | H | H | MeO | H | 50 |
| 8 | 6h | 4- MeOC ₆ H ₄ | H | H | H | H | 52 |
| 9 | 6i | 4- MeOC ₆ H ₄ | H | Me | H | H | 46 |
| 10 | 6j | C ₆ H ₅ | H | Cl | H | H | 52 |

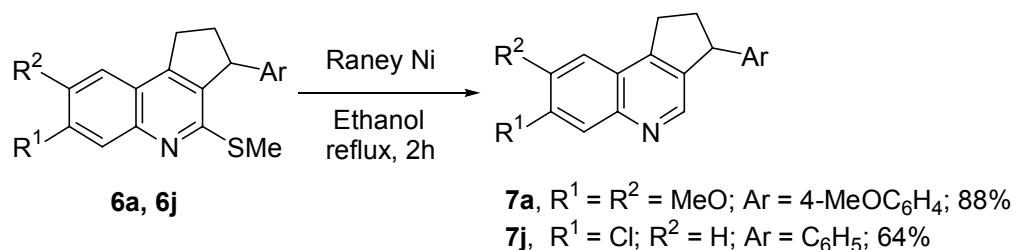
Scheme 3

The corresponding benzo[*h*]cyclopenta[*c*]quinoline (compound **6k**) could also be synthesized in moderate yield (48%) by acid induced domino- cyclization of the corresponding cyclopropyl *N,S*-acetal (compound **3k**) derived from α -naphthylamine under identical conditions (Scheme 4).



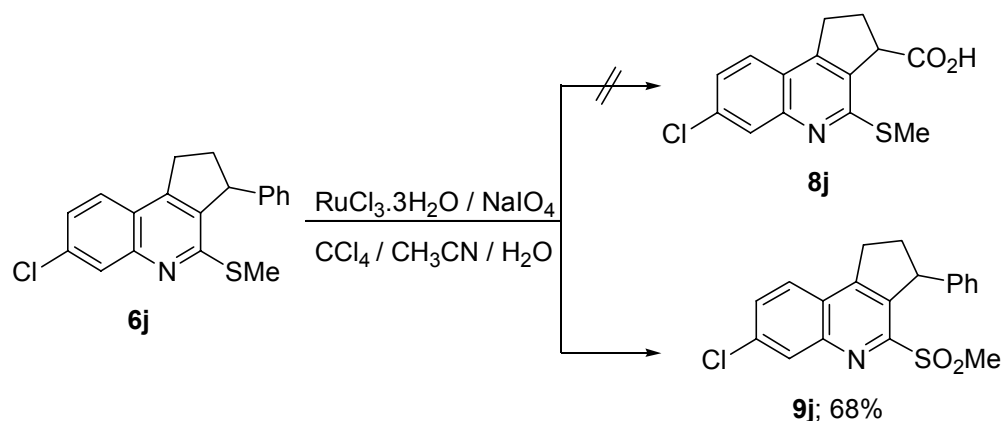
Scheme 4

Two of the 4-methylthiocyclopenta[*c*]quinolines (compounds **6a** and **6j**) were dethiomethylated in the presence of Raney nickel to afford sulfur-free cyclopenta[*c*]quinolines **7a** and **7j** in high overall yields (Scheme 5).



Scheme 5

Finally, we have also attempted ruthenium tetroxide- mediated oxidative degradation of the 3- arylcyclopenta[*c*]quinoline (compound **6j**) with a view to obtaining the corresponding cyclopenta[*c*]quinoline 3-carboxylic acid (compound **8j**) (Scheme 6). However, analysis of the reaction mixture showed the formation only of sulfone (compound **9j**) instead of compound **8j**, which could not be obtained even when excess of catalyst (8 mol. %) was taken. Our attempts in this direction are still in progress.



Scheme 6

Conclusions

In summary, we have shown that *N,S*-anilinoacetals (compound **3**) derived from 2-arylcyclopropyl ketones undergo acid-induced intramolecular domino cyclization, yielding novel substituted 3-aryl cyclopenta[*c*]quinolines (compound **6**) in 46–56% overall yield with concomitant formation of a cyclopentane and quinoline ring in a single operation.

Experimental Section

General Procedures. ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra (JEOL JNM LA-400) were recorded in CDCl_3 . TMS was used as internal reference. Melting points were obtained on Mel-Temp melting point apparatus (capillary method) and were uncorrected. The IR spectra were recorded on a Perkin Elmer 1320 spectrophotometer. The FAB mass spectra were recorded on a JEOL SX 102/DA-6000 Mass Spectrometer/Data System. Elemental analyses of the compounds were obtained using an Elementar Vario EL III Carla Erba 1108 model. Column chromatography used 100–200 mesh silica gel obtained from Acme Synthetic Chemicals (India). Substituted anilines, $\text{BF}_3 \cdot \text{OEt}_2$, SnCl_4 , TFA, H_3PO_4 (88%), $\text{Cu}(\text{OTf})_2$ and triflic acid were purchased from commercial sources. The cyclopropyl ketone **1** was prepared according to the reported procedure.^{5a}

General procedure for preparation of *N,S*-arylaminoacetals (**3a–k**)

To a stirred solution of aniline (10 mmol) in dry THF (20 mL), *n*-BuLi (15 mmol) was added, dropwise, under argon, over a period of 20 min. at $-78\text{ }^\circ\text{C}$ and the reaction mixture was stirred for 30 min. at room temperature. It was cooled to $0\text{ }^\circ\text{C}$, followed by addition of ketene *S,S*-acetal (10 mmol) in dry THF (20 mL). The reaction mixture was further stirred at room temperature for

45 minutes followed by refluxing (12–15 h) then cooled, poured into saturated NH_4Cl solution (100 mL) and extracted with CHCl_3 (3 x 25 ml). The combined organic extracts were washed with H_2O (2x50 mL), then brine (50 mL), and dried (Na_2SO_4). The solvent was evaporated (reduced pressure) to afford a crude residue, which was purified by filtration through a small silica gel column using EtOAc–hexane as eluent.

3-(3,4-Dimethoxyphenylamino)-3-methylthio-1-{2-(4-methoxyphenyl)cyclopropyl}-propenone (3a). Yield 2.80 g (70%); white solid, mp. 122–123 °C; R_f 0.50 (1:4 EtOAc–hexane); IR (KBr): 2956, 2836, 1589, 1550, 1515, 1465, 1246, 1020 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz): δ 12.73 (s, 1H, NH), 7.04 (d, J = 8.7 Hz, 2H, ArH), 6.83–6.79 (m, 4H, ArH), 6.75 (d, J = 1.7 Hz, 1H, ArH), 5.29 (s, 1H, CH), 3.86 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 2.47 (ddd, J = 9.2 Hz, 5.9 Hz, 3.7 Hz, 1H, CH), 2.30 (s, 3H, SCH_3), 1.91 (ddd, J = 7.9 Hz, 4.3 Hz, 4.3 Hz, 1H, CH), 1.65 (ddd, J = 9.2 Hz, 4.6 Hz, 4.6 Hz, 1H, CH), 1.25 (ddd, J = 8.1 Hz, 6.4 Hz, 4.2 Hz, 1H, CH); ^{13}C NMR (CDCl_3 , 100 MHz): δ 192.6, 166.1, 158.0, 148.9, 147.6, 133.5, 131.0, 127.0, 117.8, 113.8, 110.7, 109.4, 91.4, 55.91, 55.90, 55.3, 32.7, 26.7, 17.3, 14.6. Anal. Calcd. for $\text{C}_{22}\text{H}_{25}\text{NO}_4\text{S}$ (399.50): C, 66.14; H, 6.31; N, 3.51%. Found: C, 66.12; H, 6.30; N, 3.48%.

3-Methylthio-3-(*m*-tolylamino)-1-{2-(4-methoxyphenyl)cyclopropyl}propenone (3i). Yield 88% (3.10g); white solid; mp. 96–97 °C; R_f 0.50 (1:9 EtOAc–hexane); IR (KBr): 2995, 2926, 1584, 1541, 1466, 1243, 1148 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz): δ 12.95 (s, 1H, NH), 7.24 (t, J = 7.6 Hz, 1H, ArH), 7.12–7.07 (m, 4H, ArH), 7.04 (d, J = 7.6 Hz, 1H, ArH), 6.85 (d, J = 8.8 Hz, 2H, ArH), 5.37 (s, 1H, CH), 3.79 (s, 3H, OCH_3), 2.54 (ddd, J = 9.3 Hz, 6.0 Hz, 3.7 Hz, 1H, CH), 2.35 (s, 3H, CH_3), 2.33 (s, 3H, SCH_3), 1.96 (ddd, J = 8.1 Hz, 4.4 Hz, 4.4 Hz, 1H, CH), 1.72 (ddd, J = 9.0 Hz, 5.0 Hz, 4.2 Hz, 1H, CH), 1.30 (ddd, J = 9.3 Hz, 5.1 Hz, 2.5 Hz, 1H, CH); ^{13}C NMR (CDCl_3 , 100 MHz): δ 192.5, 165.0, 157.9, 138.8, 138.0, 133.4, 128.6, 126.9, 126.7, 125.4, 121.8, 113.7, 91.6, 55.1, 32.6, 26.6, 21.2, 17.2, 14.4. Anal. Calcd. for $\text{C}_{21}\text{H}_{23}\text{NO}_2\text{S}$ (353.48): C, 71.36; H, 6.56; N, 3.96%. Found: C, 71.32; H, 6.54; N, 3.94%.

General procedure for PPA- induced cyclization of *N,S*-arylaminoacetals (3a–k) to cyclopenta[*c*]quinolines (6a–k)

A mixture of *N,S*-arylaminoacetals **3** (1 mmol) and freshly prepared PPA (10 g) was heated at 90 °C for 6–10 h. The reaction mixture was cooled, neutralized with sat. NaHCO_3 solution and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 ml). The combined extracts were washed with H_2O (3 x 30 mL), brine (30 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give crude products **6** which were purified on a small silica gel column using EtOAc/hexane as eluent.

7,8-Dimethoxy-4-methylthio-3-(4-methoxyphenyl)-2,3-dihydro-1*H*-cyclopenta[*c*]quinoline (6a). Yield 0.20 g (54%); colorless solid; mp. 192–193 °C; R_f 0.40 (1:4 EtOAc–hexane); IR (KBr): 2929, 1617, 1582, 1507, 1241 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz): δ 7.40 (s, 1H, ArH), 6.98 (s, 1H, ArH), 6.96 (d, J = 8.6 Hz, 2H, ArH), 6.78 (d, J = 8.5 Hz, 2H, ArH), 4.46 (dd, J = 9.0 Hz, 3.2 Hz, 1H, CH), 4.02 (s, 3H, OCH_3), 4.0 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.29 (ddd, J = 16.4 Hz, 8.4 Hz, 8.3 Hz, 1H, CH_2), 3.14 (ddd, J = 16.6 Hz, 9.3 Hz, 3.6 Hz, 1H, CH_2), 2.74–2.67 (m, 1H, CH_2), 2.56 (s, 3H, SCH_3), 2.17–2.10 (m, 1H, CH_2); ^{13}C NMR (CDCl_3 , 100 MHz): δ 158.0, 154.6, 151.6, 148.4, 148.1, 144.5, 136.3, 135.0, 128.4, 118.6, 113.7, 107.5, 102.5, 56.04,

56.98, 55.0, 49.3, 35.4, 29.9, 12.7; MS (m/z , %): 382 ($M^+ + 1$, 77), 154 (100); Anal. Calcd. for $C_{22}H_{23}NO_3S$ (381.49): C, 69.26; H, 6.08; N, 3.67%. Found: C, 69.24; H, 6.03; N, 3.69%.

7-Methoxy-4-methylthio-3-(4-methoxyphenyl)-2,3-dihydro-1*H*-cyclopenta[*c*]quinoline (6b). Yield 56% (0.20 g). White solid; mp. 162–163 °C; R_f 0.50 (1:9 EtOAc–hexane); IR (KBr): 2927, 1617, 1586, 1508, 1413, 1225 cm^{-1} ; 1H NMR ($CDCl_3$, 400 MHz): δ 7.68 (d, $J = 8.8$ Hz, 1H, ArH), 7.36 (d, $J = 2.4$ Hz, 1H, ArH), 7.11 (dd, $J = 8.7$ Hz, 2.4 Hz, 1H, ArH), 6.98 (d, $J = 8.8$ Hz, 2H, ArH), 6.80 (d, $J = 8.5$ Hz, 2H, ArH), 4.48 (dd, $J = 8.9$ Hz, 3.3 Hz, 1H, CH), 3.96 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.34 (ddd, $J = 16.9$ Hz, 8.4 Hz, 8.4 Hz, 1H, CH_2), 3.2 (ddd, $J = 16.8$ Hz, 9.3 Hz, 3.9 Hz, 1H, CH_2), 2.79–2.69 (m, 1H, CH_2), 2.58 (s, 3H, SCH_3), 2.18–2.11 (m, 1H, CH_2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.3, 158.1, 149.5, 149.1, 136.4, 134.7, 128.4, 125.5, 118.8, 117.4, 113.8, 107.0, 55.5, 55.1, 49.3, 35.5, 29.8, 12.6; MS (m/z , %): 352 ($M^+ + 1$, 100); Anal. Calcd. for $C_{21}H_{21}NO_2S$ (351.46): C, 71.76; H, 6.02; N, 3.99%. Found: C, 71.72; H, 6.04; N, 4.00%.

7-Methoxy-4-methylthio-3-phenyl-2,3-dihydro-1*H*-cyclopenta[*c*]quinoline (6c). Yield 55% (0.18 g); brown solid; mp. 182–183 °C; R_f 0.6 (1:9 EtOAc–hexane); IR (KBr): 2913, 1616, 1586, 1500, 1415, 1303, 1227, 1148 cm^{-1} ; 1H NMR ($CDCl_3$, 400 MHz): δ 7.67 (d, $J = 9.0$ Hz, 1H, ArH), 7.28–7.18 (m, 4H, ArH), 7.12 (dd, $J = 9.0$ Hz, 2.4 Hz, 1H, ArH), 7.07 (d, $J = 1.4$ Hz, 1H, ArH), 7.05 (d, $J = 8.7$ Hz, 1H, ArH), 4.5 (dd, $J = 9.3$ Hz, 3.2 Hz, 1H, CH), 3.95 (s, 3H, OCH_3), 3.35 (ddd, $J = 16.9$ Hz, 8.4 Hz, 8.4 Hz, 1H, CH_2), 3.20 (ddd, $J = 17.0$ Hz, 9.3 Hz, 3.8 Hz, 1H, CH_2), 2.81–2.73 (m, 1H, CH_2), 2.61 (s, 3H, SCH_3), 2.21–2.15 (m, 1H, CH_2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.8, 157.7, 157.6, 144.0, 134.4, 128.5, 127.4, 126.5, 125.5, 118.7, 117.8, 117.7, 106.4, 55.6, 50.1, 35.3, 29.9, 13.0; MS (m/z , %): 322 ($M^+ + 1$, 100); Anal. Calcd. for $C_{20}H_{19}NOS$ (321.44): C, 74.73; H, 5.96; N, 4.36%. Found: C, 74.70; H, 5.98; N, 4.33%.

7-Methoxy-4-methylthio-3-(2,5-dimethoxyphenyl)-2,3-dihydro-1*H*-cyclopenta[*c*]quinoline (6d). Yield 54% (0.21 g); colorless solid, mp. 132–133 °C; R_f 0.6 (1:6 EtOAc–hexane); IR (KBr): 2930, 2830, 1618, 1586, 1499, 1485, 1418, 1280, 1219 cm^{-1} ; 1H NMR ($CDCl_3$, 400 MHz): δ 7.65 (d, $J = 8.8$ Hz, 1H, ArH), 7.37 (d, $J = 2.4$ Hz, 1H, ArH), 7.10 (dd, $J = 8.9$ Hz, 2.6 Hz, 1H, ArH), 6.85 (d, $J = 8.8$ Hz, 1H, ArH), 6.70 (dd, $J = 8.8$ Hz, 3.2 Hz, 1H, ArH), 6.17 (d, $J = 3.2$ Hz, 1H, ArH), 4.85 (dd, $J = 9.3$ Hz, 2.7 Hz, 1H, CH), 3.96 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.60 (s, 3H, OCH_3), 3.25–3.14 (m, 2H, CH_2), 2.73–2.68 (m, 1H, CH_2), 2.59 (s, 3H, SCH_3), 2.14–2.07 (m, 1H, CH_2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.3, 157.6, 153.5, 151.4, 150.0, 149.5, 133.9, 133.6, 125.4, 118.9, 117.3, 114.5, 111.6, 110.7, 106.9, 56.3, 55.5, 55.4, 43.2, 33.9, 29.7, 12.5; MS (m/z , %): 382 ($M^+ + 1$, 100); Anal. Calcd. for $C_{22}H_{23}NO_3S$ (381.49): C, 69.26; H, 6.08; N, 3.67%. Found: C, 69.21; H, 6.12; N, 3.69%.

6,9-Dimethoxy-4-methylthio-3-phenyl-2,3-dihydro-1*H*-cyclopenta[*c*]quinoline (6e). Yield 51% (0.18 g); brown solid; mp. 120–121 °C; R_f 0.4 (1:9 EtOAc–hexane); IR (KBr): 2928, 1607, 1584, 1560, 1465, 1258, 1107 cm^{-1} ; 1H NMR ($CDCl_3$, 400 MHz): δ 7.23 (t, $J = 6.8$ Hz, 2H, ArH), 7.18 (t, $J = 7.2$ Hz, 1H, ArH), 7.03 (d, $J = 7.0$ Hz, 2H, ArH), 6.94 (d, $J = 8.6$ Hz, 1H, ArH), 6.67 (d, $J = 8.6$ Hz, 1H, ArH), 4.46 (dd, $J = 9.5$ Hz, 2.7 Hz, 1H, CH), 4.02 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 3.62–3.58 (m, 2H, CH_2), 2.70–2.62 (m, 4H, SCH_3 + 1H, CH_2), 2.14–2.07

(m, 1H, CH₂); ¹³C NMR (CDCl₃, 100 MHz): δ 157.0, 150.8, 149.1, 148.9, 144.2, 140.8, 136.8, 128.4, 127.4, 126.3, 117.6, 108.6, 103.1, 56.9, 55.5, 48.9, 35.3, 34.1, 12.4; MS (*m/z*, %): 352 (M⁺+1, 100); Anal. Calcd. for C₂₁H₂₁NO₂S (351.46): C, 71.76; H, 6.02; N, 3.99%. Found: C, 71.71; H, 6.07; N, 4.00%.

6,9-Dimethoxy-4-methylthio-3-(3,4-dimethoxyphenyl)-2,3-dihydro-1*H*-cyclopenta[*c*]-quinoline (6f). Yield 54% (0.22 g); white solid; mp. 144–145 °C; R_f 0.4 (1:3 EtOAc–hexane); IR (KBr): 2945, 2932, 1585, 1563, 1498, 1218 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 6.94 (d, *J* = 8.6 Hz, 1H, ArH), 6.72 (d, *J* = 8.3 Hz, 1H, ArH), 6.68 (d, *J* = 8.5 Hz, 1H, ArH), 6.60 (d, *J* = 1.9 Hz, 1H, ArH), 6.54 (dd, *J* = 8.3 Hz, 2.0 Hz, 1H, ArH), 4.42 (dd, *J* = 9.3 Hz, 3.2 Hz, 1H, CH), 4.02 (s, 3H, OCH₃), 3.90 (s, 3H, OCH₃), 3.83 (s, 3H, OCH₃), 3.78 (s, 3H, OCH₃), 3.60–3.57 (m, 2H, CH₂), 2.71–2.61 (m, 4H, SCH₃ + 1H, CH₂), 2.12–2.05 (m, 1H, CH₂); ¹³C NMR (CDCl₃, 100 MHz): δ 157.1, 150.8, 149.1, 149.0, 147.5, 140.7, 136.9, 136.8, 119.3, 117.6, 110.84, 110.8, 108.5, 103.1, 56.8, 55.8, 55.7, 55.5, 48.7, 35.5, 34.0, 12.5; MS (*m/z*, %): 412 (M⁺+1, 100); Anal. Calcd. for C₂₃H₂₅NO₄S (411.51): C, 67.13; H, 6.12; N, 3.40%. Found: C, 67.10; H, 6.16; N, 3.44%.

8-Methoxy-4-methylthio-3-(4-methoxyphenyl)-2,3-dihydro-1*H*-cyclopenta[*c*]quinoline (6g). Yield 50% (0.18 g); white solid; mp. 152–153 °C; R_f 0.60 (1:9 EtOAc–hexane); IR (KBr): 2921, 1617, 1576, 1550, 1508, 1458, 1242, 1031 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 7.93 (d, *J* = 7.3 Hz, 1H, ArH), 7.29 (dd, *J* = 9.0 Hz, 2.7 Hz, 1H, ArH), 7.03 (d, *J* = 2.7 Hz, 1H, ArH), 6.98 (dd, *J* = 8.5 Hz, 1.7 Hz, 2H, ArH), 6.80 (dd, *J* = 8.5 Hz, 1.7 Hz, 2H, ArH), 4.49 (dd, *J* = 9.0, 3.2 Hz, 1H, CH), 3.93 (s, 3H, OCH₃), 3.76 (s, 3H, OCH₃), 3.60–3.30 (m, 1H, CH₂), 3.18 (ddd, *J* = 16.7 Hz, 9.4 Hz, 3.7 Hz, 1H, CH₂), 2.78–2.72 (m, 1H, CH₂), 2.57 (s, 3H, SCH₃), 2.19–2.14 (m, 1H, CH₂); ¹³C NMR (CDCl₃, 100 MHz): δ 158.2, 156.8, 154.5, 148.2, 143.7, 137.0, 136.2, 129.6, 128.4, 124.7, 120.5, 113.8, 102.9, 55.5, 55.1, 49.5, 35.4, 29.9, 12.6; MS (*m/z*, %): 352 (M⁺+1, 100), 154 (97); Anal. Calcd. for C₂₁H₂₁NO₂S (351.46): C, 71.76; H, 6.02; N, 3.99%. Found: C, 71.78; H, 6.00; N, 3.96%.

4-Methylthio-3-(4-methoxyphenyl)-2,3-dihydro-1*H*-cyclopenta[*c*]quinoline (6h). Yield 55% (0.17 g); viscous liquid; R_f 0.70 (1:9 EtOAc–hexane); IR (KBr): 2922, 1588, 1473, 1559, 1473, 1214, 1147 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 7.92 (d, *J* = 8.3 Hz, 1H, ArH), 7.71 (d, *J* = 8.0 Hz, 1H, ArH), 7.55 (td, *J* = 7.6 Hz, 1.4 Hz, 1H, ArH), 7.38 (td, *J* = 6.95 Hz, 1.2 Hz, 1H, ArH), 6.91 (dd, *J* = 7.8 Hz, 2.0 Hz, 2H, ArH), 6.72 (dd, *J* = 7.8 Hz, 2.2 Hz, 2H, ArH), 4.43 (d, *J* = 9.0 Hz, 1H, CH), 3.69 (s, 3H, OCH₃), 3.33–3.27 (m, 1H, CH₂), 3.18–3.16 (m, 1H, CH₂), 2.71–2.65 (m, 1H, CH₂), 2.51 (s, 3H, SCH₃), 2.09–2.06 (m, 1H, CH₂); ¹³C NMR (CDCl₃, 100 MHz): δ 158.2, 157.5, 149.0, 147.8, 136.7, 136.2, 128.7, 128.5, 128.2, 124.9, 124.4, 124.0, 113.8, 55.1, 49.5, 35.4, 29.8, 12.6; MS (*m/z*, %): 322 (M⁺+1, 100), 154 (80). Anal. Calcd. for C₂₀H₁₉NOS (321.44): C, 74.73; H, 5.96; N, 4.36%. Found: C, 74.74; H, 5.92; N, 4.33%.

7-Methyl-4-methylthio-3-(4-methoxyphenyl)-2,3-dihydro-1*H*-cyclopenta[*c*]quinoline (6i). Yield 46% (0.15 g); colorless solid; mp. 126–127 °C; R_f 0.60 (1:9 EtOAc–hexane); IR (KBr): 2920, 1584, 1509, 1297, 1246 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 7.78 (s, 1H, ArH), 7.60 (d, *J* = 8.3 Hz, 1H, ArH), 7.23 (dd, *J* = 8.3 Hz, 1.2 Hz, 1H, ArH), 6.91 (d, *J* = 8.5 Hz, 2H, ArH), 6.73

(d, $J = 8.8$ Hz, 2H, ArH), 4.42 (dd, $J = 9.0$ Hz, 2.9 Hz, 1H, CH), 3.70 (s, 3H, OCH₃), 3.29 (ddd, $J = 16.8$ Hz, 8.5 Hz, 8.4 Hz, 1H, CH₂), 3.13 (ddd, $J = 16.9$ Hz, 9.3 Hz, 3.8 Hz, 1H, CH₂), 2.72–2.62 (m, 1H, CH₂), 2.53 (s, 3H, SCH₃), 2.48 (s, 3H, CH₃), 2.12–2.05 (m, 1H, CH₂); ¹³C NMR (CDCl₃, 100 MHz): δ 158.0, 157.3, 149.0, 147.8, 139.0, 136.2, 135.9, 128.4, 127.2, 127.0, 124.0, 121.8, 113.8, 55.0, 49.4, 35.4, 29.8, 21.8, 12.6; MS (m/z , %): 336 ($M^+ + 1$, 100). Anal. Calcd. for C₂₁H₂₁NOS (335.46): C, 75.19; H, 6.31; N, 4.18%. Found: C, 75.15; H, 6.35; N, 4.21%.

7-Chloro-4-methylthio-3-phenyl-2,3-dihydro-1H-cyclopenta[c]quinoline (6j). Yield 52% (0.17 g); light yellow solid; mp. 132–133 °C; R_f 0.60 (1:8 EtOAc–hexane); IR (KBr): 2924, 1605, 1582, 1508, 1488, 1294, 1029 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 8.01 (s, 1H, ArH), 7.65 (d, $J = 8.8$ Hz, 1H, ArH), 7.36 (dd, $J = 8.7$ Hz, 1.6 Hz, 1H, ArH), 7.24 (t, $J = 7.0$ Hz, 2H), 7.18 (t, $J = 6.6$ Hz, 1H, ArH), 7.03 (d, $J = 7.8$ Hz, 2H, ArH), 4.48 (dd, $J = 9.0$ Hz, 2.9 Hz, 1H, CH), 3.34 (ddd, $J = 16.8$ Hz, 8.4 Hz, 8.3 Hz, 1H, CH₂), 3.17 (ddd, $J = 17.0$ Hz, 9.4 Hz, 3.8 Hz, 1H, CH₂), 2.80–2.70 (m, 1H, CH₂), 2.54 (s, 3H, SCH₃), 2.21–2.13 (m, 1H, CH₂); ¹³C NMR (CDCl₃, 100 MHz): δ 159.0, 149.5, 147.6, 143.6, 136.7, 134.7, 128.5, 127.4, 126.8, 126.6, 125.8, 125.6, 122.2, 50.2, 35.1, 29.9, 12.9; MS (m/z , %): 327 ($M^+ + 1$, 64), 326 (M^+ , 100); Anal. Calcd. for C₁₉H₁₆ClNS (325.86): C, 70.03; H, 4.95; N, 4.30%. Found: C, 70.06; H, 4.93; N, 4.27%.

6-Methylthio-7-(4-methoxyphenyl)-8,9-dihydro-7H-benzo[h]cyclopenta[c]quinoline (6k).

Yield 48% (0.18 g); colorless solid; mp. 102–103 °C; R_f 0.70 (1:7 EtOAc–hexane); IR (KBr): 2924, 1582, 1508, 1431, 1245, 1029 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 9.23 (d, $J = 8.1$ Hz, 1H, ArH), 7.82 (dd, $J = 8.0$ Hz, 1.4 Hz, 1H, ArH), 7.69 (d, $J = 8.8$ Hz, 1H, ArH), 7.64 (d, $J = 8.8$ Hz, 1H, ArH), 7.58 (t, $J = 7.9$ Hz, 2H, ArH), 6.94 (d, $J = 8.8$ Hz, 2H, ArH), 6.74 (d, $J = 8.8$ Hz, 2H, ArH), 4.47 (dd, $J = 9.0$ Hz, 3.4 Hz, 1H, CH), 3.69 (s, 3H, OCH₃), 3.36 (ddd, $J = 18.7$ Hz, 10.3 Hz, 8.3 Hz, 1H, CH₂), 3.21 (ddd, $J = 16.8$ Hz, 9.2 Hz, 4.0 Hz, 1H, CH₂), 2.80–2.67 (m, 4H, SCH₃ + 1H CH₂), 2.17–2.09 (m, 1H, CH₂); ¹³C NMR (CDCl₃, 100 MHz): δ 158.2, 155.6, 149.9, 144.9, 137.4, 136.0, 133.5, 131.1, 128.5, 127.8, 127.6, 126.7, 126.0, 124.7, 122.2, 120.9, 113.8, 55.1, 49.4, 35.6, 30.0, 13.1; MS (m/z , %): 372 ($M^+ + 1$, 86), 154 (100); Anal. Calcd. for C₂₄H₂₁NOS (371.49): C, 77.59; H, 5.70; N, 3.77%. Found: C, 77.57; H, 5.72; N, 3.74%.

General procedure for Raney Ni de-thiomethylation of quinolines 6a and 6j

A suspension of quinoline (**6a** or **6j**) (1 mmol) and Raney Ni (W2) (ca. 1 g) in ethanol (20 ml) was heated at reflux with stirring for 3 h (monitored by TLC). It was then filtered through a sintered glass funnel and washed with hot ethanol. The filtrate was concentrated to afford a viscous residue, which was purified by column chromatography over silica gel using EtOAc–hexane (1:3) as eluent to give the pure products (**7a**, **7j**).

7,8-Dimethoxy-3-(4-methoxyphenyl)-2,3-dihydro-1H-cyclopenta[c]quinoline (7a). Yield 88% (0.29 g); colorless solid; mp. 116–117 °C; R_f 0.5 (1:3, EtOAc:hexane); ¹H NMR (CDCl₃, 300 MHz): δ 8.37 (s, 1H, ArH), 7.47 (s, 1H, ArH), 7.10 (d, $J = 8.4$ Hz, 2H, ArH), 7.03 (s, 1H, ArH), 6.86 (d, $J = 8.4$ Hz, 2H, ArH), 4.55 (t, $J = 8.0$ Hz, 1H, CH), 4.04 (s, 3H, OCH₃), 4.03 (s, 3H, OCH₃), 3.80 (s, 3H, OCH₃), 3.37 (ddd, $J = 16.5$ Hz, 9.0 Hz, 4.1 Hz, 1H, CH₂), 3.16 (ddd, $J = 16.5$ Hz, 8.1 Hz, 8.1 Hz, 1H, CH₂), 2.84–2.72 (m, 1H, CH₂), 2.22–2.09 (m, 1H, CH₂); ¹³C NMR

(CDCl₃, 75 MHz): δ 158.3, 151.7, 149.8, 148.5, 145.9, 144.0, 137.8, 137.0, 128.7, 121.1, 114.0, 108.5, 101.9, 56.03, 56.02, 55.3, 49.6, 36.2, 29.9; MS (ES, *m/z*, %): 336 (M⁺+1, 100); Anal. Calcd. for C₂₁H₂₁NO₃ (335.40): C, 75.20; H, 6.31; N, 4.18%. Found: C, 75.26; H, 6.29; N, 4.13%.

Procedure for ruthenium tetroxide oxidation of 7-chloro-4-methylthio-3-phenyl-2,3-dihydro-1*H*-cyclopenta[*c*]quinoline (6j)

To a solution of quinoline **6j** (1.0 mmol) in CCl₄–CH₃CN (8 mL, 1:1), sodium periodate (10 mmol) was added with vigorous stirring followed by addition of a solution of RuCl₃·3H₂O (8 mol. %) in water (4 mL). Reaction mixture was stirred for 20 min. (monitored by TLC) and worked-up by addition of water (10 mL) to dissolve the separated sodium iodate. The aqueous layer was extracted with CH₂Cl₂ (3x20 mL) and the combined extracts were washed with H₂O (3x30 mL), brine (30 mL), dried (Na₂SO₄) and filtered through Celite. The solvent was evaporated under reduced pressure to give crude product **9j**, which was purified using a small silica gel column using EtOAc/hexane (1:3) as eluent.

7-Chloro-4-methanesulfonyl-3-phenyl-2,3-dihydro-1*H*-cyclopenta[*c*]quinoline, 9j. Yield 68% (0.24 g); colorless solid, mp. 174–175 °C; R_f 0.6 (1:3 EtOAc:hexane); IR (KBr): 2999, 2919, 1606, 1314, 1337, 1073 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz): δ 8.25 (s, 1H, ArH), 7.91 (d, *J* = 8.7 Hz, 1H, ArH), 7.69 (d, *J* = 8.7 Hz, 1H, ArH), 7.26–7.16 (m, 3H, ArH), 6.97 (d, *J* = 6.9 Hz, 2H, ArH), 5.32 (d, *J* = 9.0 Hz, 1H, CH), 3.54–3.33 (m, 2H, CH₂), 2.94 (s, 3H, CH₃), 2.90–2.77 (m, 1H, CH₂), 2.37–2.31 (m, 1H, CH₂); ¹³C NMR (CDCl₃, 75 MHz): δ 156.2, 155.2, 146.5, 144.4, 136.4, 136.0, 130.2, 129.4, 128.5, 127.3, 126.7, 125.9, 125.4, 49.6, 40.2, 35.2, 29.6; MS (ES, *m/z*, %): 358 (M⁺+1, 100); Anal. Calcd. for C₁₉H₁₆ClNO₂S (357.85): C, 63.77; H, 4.51; N, 3.91%. Found: C, 63.74; H, 4.53; N, 3.94%.

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