A Facile Synthesis of 1-Alkyl-5-arylalkoxy-6-methoxy-3,4-dihydroisoquinolines

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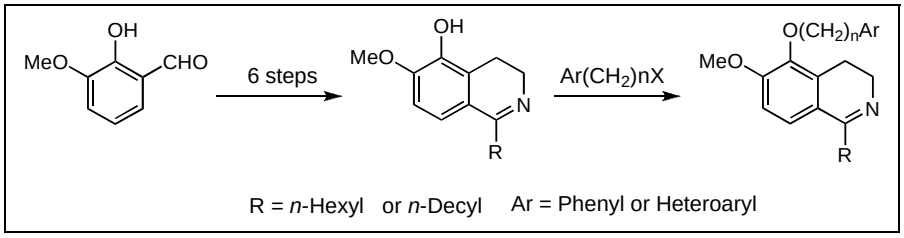

1-Alkyl-5-arylalkoxy-6-methoxy-3,4-dihydroisoquinolines were synthesized by the alkylation of 1-alkyl-5-hydroxy-6-methoxy-3,4-dihydroisoquinolines with arylalkyl halide in the presence of potassium carbonate. 1-Alkyl-5-hydroxy-6-methoxy-3,4-dihydroisoquinolines as key precursor prepared from *o*-vaniline *via* 6 steps.

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INTRODUCTION

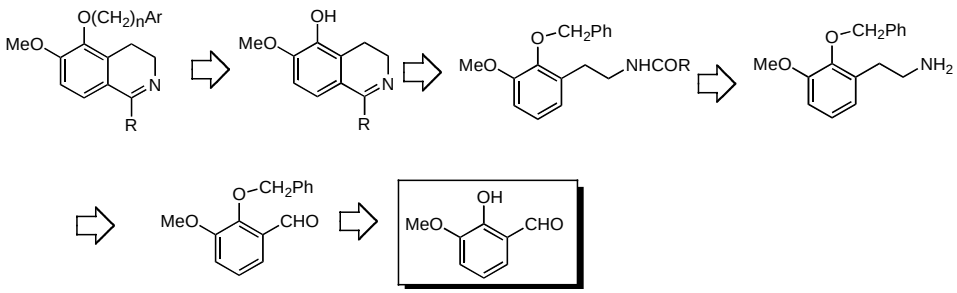
Isoquinoline alkaloids are often selected as synthetic targets due to their various physiological activities and structural properties [1]. In previous papers [2], we reported the pharmacological effect and chemistry for some isoquinoline derivatives. In connection with the SAR study and the evaluation of biological activity such as cardiovascular activity or immunosuppressive activity, we required especially some 1-alkyl-5-arylalkoxy (or heteroarylalkoxy)-6-methoxy-3,4-dihydroisoquinoline derivatives. Although the synthetic methods of the interesting isoquinolines have been reported [1-3], there are no general synthetic methods to obtain 1-alkyl-5-arylalkoxy-6-methoxy-3,4-dihydroisoquinolines. The Bischler-Napieralski [2-4] condensation is a common method for the formation of 3,4-dihydroisoquinoline ring system.

According to the retrosynthesis as shown Scheme 1, the two routes are possible for the synthesis of 1-alkyl-5-arylalkoxy-3,4-dihydroisoquinolines; the first is the method using the alkylation of 1-alkyl-5-hydroxy derivative with arylalkyl halide (method A), and the second is the method using the cyclization of *N*-(2-alkoxy-3-methoxyphenethyl)alkanamide (method B).

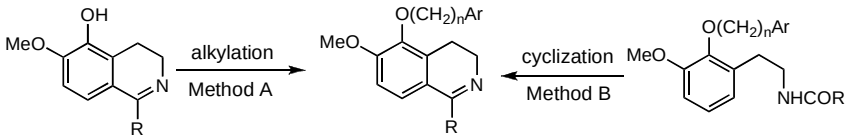
The method A is more useful than the method B for the introduction of various arylalkoxy groups at C-5 position (Scheme 2). When 2-heteroalkoxy-3-methoxybenzaldehyde is used as the starting material (method B), unexpected side reactions may occur during the coupling reaction and the cyclization. Actually, we detected the unknown products on tlc during these reaction. Therefore, we attempted to synthesize the 1-alkyl-5-arylalkoxy-3,4-dihydroisoquinolines according to method A.

From the retrosynthesis of target molecules (Scheme 1), we chose *o*-vaniline (**1**) as the starting material for the

Scheme 1



Scheme 2



synthesis of 1-alkyl-5-hydroxy-6-methoxy derivatives as a key precursor.

In this paper, we would like to report on synthesis of some 1-alkyl-5-arylalkoxy-6-methoxy-3,4-dihydroisoquinolines from *o*-vaniline.

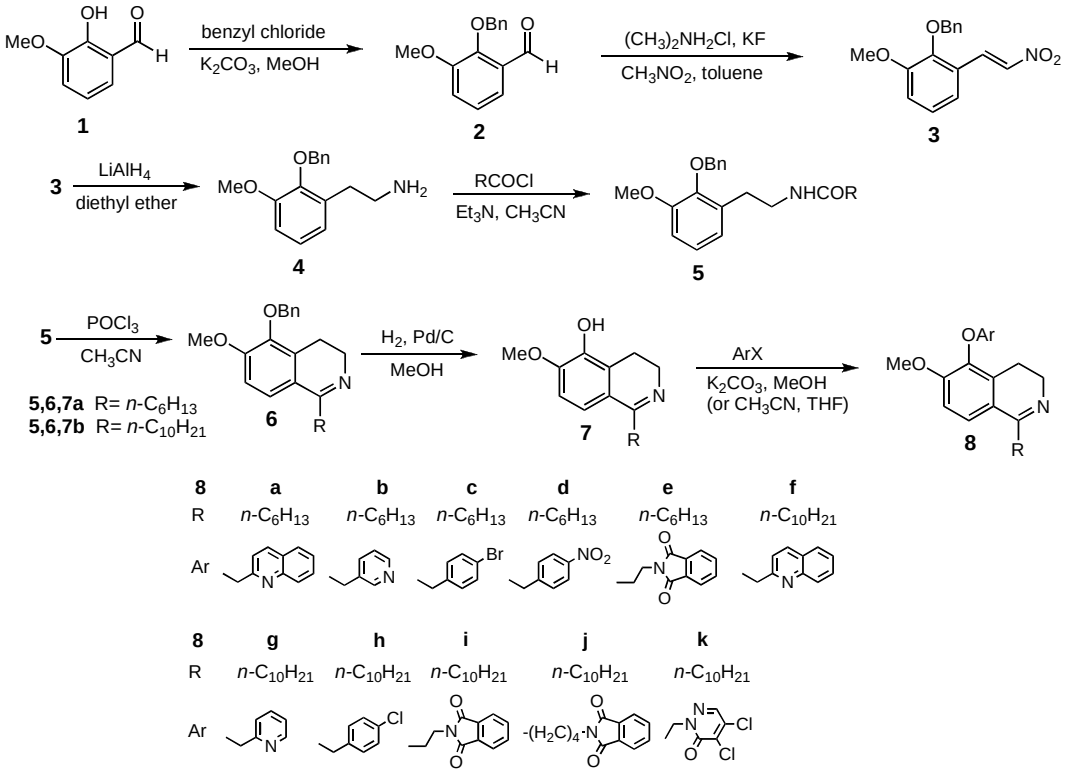
RESULTS AND DISCUSSION

Compound **7** as key precursor was prepared from *o*-vaniline (**1**) *via* six steps according to Scheme 3. Reaction of *o*-vaniline (**1**) with benzyl chloride in the presence of potassium carbonate in methanol gave compound **2** in 93% yield. Treatment of **2** with nitromethane in the presence of potassium fluoride and dimethylamine hydrochloride in toluene afforded β-nitrostyrene **3** in excellent yield. Compound **3** was reduced selectively to the corresponding amine **4** using lithium aluminum hydride in diethyl ether. Reaction of **4** with acyl chloride in the presence of triethylamine in acetonitrile gave the corresponding amides **5a** and **5b** in excellent yields. Cyclization of **5** with phosphorus oxychloride in acetonitrile at room temperature also furnished the corresponding 3,4-dihydroisoquinolines **6a** and **6b**. The infrared spectra of **6** did not show absorption bands of the carbonyl and NH bonds. The ^{1}H nmr spectra of **6** revealed proton signals of one OCH_3, two CH_2 of C-3 and C-4 positions and one benzylic CH_2 at C-5 involving aromatic and alkyl chain protons at C-1 position.

Debenzylation of compound **6** with hydrogen in the presence of Pd/C in methanol gave the corresponding 5-hydroxy-3,4-dihydroisoquinolines **7a** and **7b** in good yield, respectively. The infrared spectra of **7a** and **7b** showed absorption band of the hydroxyl bond. The ^{1}H nmr spectra of **7a** and **7b** also detected proton signals of one OCH_3 and two CH_2 of C-3 and C-4 positions involving aromatic and alkyl chain protons at C-1 position.

On the other hand, we attempted to synthesize some 5-arylalkoxy (or heteroarylalkoxy)-3,4-dihydroxyiso-

Scheme 3



quinolines. Alkylation of compound **7** with benzyl chlorides or heteroarylalkyl chlorides (or bromides) in the presence of potassium carbonate in methanol except for **8c** (CH_3CN), **8h** (CH_3CN) and **8k** (THF) afforded the corresponding 1-hexyl (or decyl)-5-arylalkoxy-6-methoxy-3,4-dihydroisoquinolines in moderate to good yield, respectively. When the reaction of **7** with 4,5-dichloro-1-chloromethylpyridazin-3(2*H*)-one in the presence of potassium carbonate in methanol, 4-chloro-5-methoxy-1-methoxymethylpyridazin-3(2*H*)-one as the main product was obtained instead of the expected product **8k**. This result is similar to Chung's result for the methoxylation of 4,5-dichloropyridazin-3(2*H*)-one with potassium carbonate in methanol [5]. Therefore, we used tetrahydrofuran as solvent for the alkylation of compound **7** with 4,5-dichloro-1-chloromethylpyridazin-3(2*H*)-one in the presence of potassium carbonate. The infrared spectra of **8** did not show absorption band of the OH bond. The ^{1}H nmr spectra of **8** revealed proton signals of one OCH_3 (δ 3.58 – 3.92 ppm as singlet) and two CH_2 of C-3 and C-4 positions (δ 2.43 – 2.75 ppm as triplets or multiplets for C-3 and δ 2.33- 2.66 ppm as triplets or multiplets for C-4) involving aromatic, arylalkyl chain at C-5 and alkyl chain protons at C-1 position. The structures of all synthetic compounds were established by ir, nmr and elemental analyses.

In summary, a efficient and facile route for the preparation of 1-alky-5-arylalkoxy-6-methoxy-3,4-dihydroisoquinolines has been developed. The most advantageous feature of the synthesis reported here is the fact that the target molecules can be obtained with various arylalkoxy group at C-5 position in 3,4-dihydroisoquinoline ring. Further work including the biological activity and the chemical transformation of the products to 2-substituted-1,2,3,4-tetraisoquinolinium salts are under way in our laboratory.

EXPERIMENTAL

Melting points were determined with a capillary apparatus and uncorrected.^{1}H and ^{13}C NMR spectra were recorded on a 300 MHz spectrophotometer with chemical shift values reported in δ units (ppm) relative to an internal standard (TMS). IR spectra were obtained on an IR spectrophotometer. Elemental analyses were performed with a CHNS-932 (Leco). High resolution mass spectra (HRMS) were obtained on a JEOL JMS-700 (Japan) system. Open-bed chromatography was carried out on silica gel (70-230 mesh, Merck) using gravity flow. The column was packed as slurries with the elution solvent.

2-(Benzyloxy)-3-methoxybenzaldehyde (2). A solution of *o*-vaniline (**1**, 10 g, 66 mmol), potassium carbonate (11 g, 79 mmol) and benzyl chloride (11.4 mL, 99 mmol) in methanol (200 mL) was refluxed for 17-19 hours. After cooling to room temperature, the mixture was filtrated and evaporated under reduced pressure. Water (150 mL) and diethyl ether (150 mL) was added to the resulting residue and the mixture was then stirred for 5 minutes. After separating the organic layer, this layer was washed with sodium hydroxide solution (100 mL, 25%) and water (150 mL) and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give compound **2** as yellowish liquid in 93% yield. mp oil (lit.[6] mp 58 - 59 °C). IR (KBr): 3060, 3030, 2940, 2870, 1690, 1590, 1480, 1450, 1370, 1310, 1270, 1220, 1180, 1070, 970, 910, 670 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.79 (s, 3H), 5.21 (s, 2H), 7.02 – 7.09 (m, 2H), 7.27 – 7.35 (m, 6H), 10.23 ppm (s, 1H); ^{13}C NMR ($CDCl_3$): δ 118.1, 118.9, 124.3, 128.4, 128.5, 128.6, 128.7, 130.3, 136.6, 153.1, 190.1 ppm; *Anal.* Calcd. for $C_{15}H_{14}O_3$: C , 74.36; H 5.82. Found: C, 74.40; H 5.89.

2-(Benzyloxy)-1-methoxy-3-(2-nitrovinyl)benzene (3). Compound **2** (2 g, 8.3 mmol) was dissolved in toluene/ nitromethane (20 mL: 20 mL). *N,N*-Dimethylammonium chloride (1.4 g, 16.6 mmol) and potassium fluoride (0.1 g, 1.3 mmol) were added to the solution. The mixture was refluxed for 3-4 hours. And during the reaction, water was removed using Dean-Stark tube. After cooling to room temperature, the solution was filtrated and evaporated under reduced pressure. The resulting residue was dissolved in diethyl ether (30 mL) after which the solution was filtrated. The solvent was evaporated under reduced pressure to give the product **3** as yellow crystals in 89% yield, mp 64-65°C (lit.[6] mp 72 – 73°C). IR (KBr): 3110, 3080, 3010, 2940, 2880, 2840, 1680, 1630, 1580, 1510, 1450, 1340, 1270, 1060, 970, 790, 740 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.96 (s, 3H), 5.13 (s, 2H), 7.02 – 7.15 (m, 3H), 7.34 - 7.40 (m, 6H), 7.57 (d, 1H, J = 13.7 Hz), 8.11 ppm (d, 1H, J = 13.7 Hz); ^{13}C NMR ($CDCl_3$): δ 56.0, 75.7, 115.7, 120.7, 124.6, 125.0, 127.0, 128.6, 128.9, 134.7, 136.3, 138.1, 147.7, 153.3 ppm. *Anal.* Calcd. for $C_{16}H_{15}NO_4$(285.29): C, 67.36; H, 5.30; N 4.91. Found: C, 67.41; H, 5.39; N, 5.02.

2-[2-(Benzyloxy)-3-methoxyphenyl]ethanamine (4). A ether solution of compound **3** (10 g, 25.1 mmol in 100 mL of diethyl ether) was added slowly to ether solution of lithium aluminum hydride (6.7 g, 0.18 mol in 200 mL of diethyl ether) for 30 minutes with stirring. The mixture was refluxed for 44 - 46 hours. After cooling the reaction mixture to room temperature, water (50 mL) was added slowly in an ice bath. And potassium hydroxide aqueous solution (20 mL, 20%) was then added to the mixture. The mixture was stirred for 5 minutes, and neutralized by adding hydrochloric acid (50%) to pH 7. The product was extracted with diethyl ether (2 x 250 mL). The resulting ether solution was washed with water (250 mL) and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give compound **4** as liquid in 77% yield. IR (KBr): 3370, 3300, 3060, 2940, 2870, 2840, 1590, 1470, 1380, 1270, 1210, 1080, 1010, 990, 750, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.13 (bs, 2H), 2.70 (t, 2H, J = 6.8 Hz), 2.85 (t, 2H, J = 6.8 Hz), 3.85 (s, 3H), 4.99 (s, 2H), 6.75-6.82 (m, 2H), 6.99 (t, 1H, J = 7.9 Hz), 7.30 – 7.38 (m, 3H), 7.45 ppm (d, 2H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$): δ 34.2, 42.6, 55.7, 74.7 110.7, 122.3, 124.0, 127.9, 128.1, 128.4, 133.8, 138.0, 146.2, 152.9 ppm. *Anal.* Calcd. for $C_{16}H_{19}NO_2$: C, 74.68; H ,7.44; N, 5.44. Found: C, 74.71; H, 7.49; N, 5.47.

***N*-(2-Benzyloxy-3-methoxyphenethyl)alkanamide (5).** A solution of compound **4** (5 g, 19.4 mmol), triethyl amine (3.3 mL, 23.28 mmol), alkanoyl chloride (23.28 mmol) and acetonitrile (150 mL) was stirred for 1 -1.5 hours at room temperature. After filtering the mixture, the solvent was evaporated under reduced pressure. Diethyl ether/ water (100 mL: 100 mL) was added to the residue. The resulting solution

was stirred for 5 minute. After separating the organic layer, the solution was dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give the product **5**.

Compound 5a. Yield: 93%; mp 49-50°C. IR (KBr): 3300, 3070, 3030, 2950, 2930, 2860, 1640, 1570, 1550, 1470, 1370, 1270, 1210, 1080, 990, 750, 700 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.88 (t, 3H, J = 6.6 Hz), 1.21 – 1.29 (m, 6H), 1.50 (m, 2H), 2.00 (t, 2H, J = 7.4 Hz), 2.78 (t, 2H, J = 6.7 Hz), 3.42 (q, 2H, J = 6.3 and 6.1 Hz), 3.90 (s, 3H), 5.04 (s, 2H), 5.95 (s, NH), 6.77 (d, 1H, J = 7.6 Hz), 6.86 (d, 1H, J = 8.0 Hz), 7.03 (t, 1H, J = 7.9 Hz), 7.32 – 7.42 (m, 3H), 7.48 ppm (d, 2H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$): δ 14.1, 22.5, 25.6, 28.9, 30.0, 31.5, 36.7, 40.6, 55.7, 74.8, 111.0, 122.4, 124.4, 128.1, 128.3, 128.5, 133.4, 137.7, 145.9, 152.8, 173.3 ppm. *Anal.* Calcd. for $C_{23}H_{31}NO_3$: C, 74.76; H, 8.46; N, 3.79. Found: C, 74.80; H, 8.60; N 3.83.

Compound 5b. Yield: 89%; mp 70-71°C. IR (KBr): 3320, 3080, 3040, 3000, 2920, 2850, 1640, 1580, 1550, 1470, 1380, 1360, 1310, 1270, 1210, 1090, 1040, 1000, 980, 920, 750, 700 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.88 (t, 3H, J = 6.9 Hz), 1.20 – 1.32 (m, 14H), 1.43 – 1.52 (m, 2H), 1.98 (t, 2H, J = 7.4 Hz), 2.76 (t, 2H, J = 6.5 Hz), 3.38 – 3.44 (m, 2H), 3.90 (s, 3H), 5.02 (s, 2H), 5.85 (bs, 1H, D_2O exchangeable), 6.76 (d, 1H, J = 7.6 Hz), 6.85 (d, 1H, J = 8.1 Hz), 7.03 (t, 1H, J = 8.1 Hz), 7.31 – 7.41 (m, 3H), 7.46 ppm (d, 2H, J = 6.7 Hz); ^{13}C NMR ($CDCl_3$): δ 14.1, 22.7, 25.7, 29.2, 29.3, 29.4, 29.5, 29.6, 30.0, 31.9, 36.8, 40.6, 55.7, 74.8, 110.9, 122.4, 124.4, 128.1, 128.3, 128.5, 133.5, 137.6, 145.9, 152.8, 173.2 ppm. *Anal.* Calcd. for $C_{27}H_{39}NO_3$: C, 76.20; H, 9.24; N, 3.29. Found: C, 76.28; H, 9.31; N, 3.30.

1-Alkyl-5-benzyloxy-6-methoxy-3,4-dihydroisoquinoline (6). A solution of compound **5** (0.027 mol), phosphorus oxychloride (10.1 mL, 0.108 mol) and acetonitrile (150 mL) was stirred for 18 hours at room temperature. After evaporating the solvent under reduced pressure, water (100 mL) was added to the residue. And the mixture was then neutralized with sodium hydroxide solution (20%) to pH 7. The product was extracted with diethyl ether (100 mL x 2). After drying over anhydrous magnesium sulfate, the solvent was evaporated under reduced pressure to give the product **6**.

Compound 6a. Yield 74%; mp 137 - 138°C. IR (KBr): 3070, 3020, 2930, 2850, 1600, 1570, 1470, 1280, 1220, 1080, 980, 750, 700 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.87 (t, 3H, J = 6.8 Hz), 1.27 – 1.32 (m, 4H), 1.38 – 1.48 (m, 2H), 1.70 – 1.79 (m, 2H), 2.75 (t, 2H, J = 7.7 Hz), 3.21 (t, 2H, J = 7.7 Hz), 3.60 (t, 2H, J = 7.6 Hz), 4.08 (s, 3H), 5.06 (s, 2H), 7.12 (d, 1H, J = 8.8 Hz), 7.30 – 7.36 (m, 5H), 7.67 ppm (d, 1H, J = 8.8 Hz); ^{13}C NMR ($CDCl_3$): δ 13.9, 19.7, 22.2, 28.8, 29.1, 31.2, 32.4, 40.3, 56.5, 74.9, 111.3, 117.6, 127.9, 128.5, 128.6, 128.7, 132.1, 136.2, 143.9, 159.8, 177.4 ppm; HRMS Calcd. for $C_{23}H_{29}NO_2$: 351.2198; Found: 351.2194. *Anal.* Calcd. for $C_{23}H_{29}NO_2$: C, 78.59; H, 8.32; N, 3.99. Found: C, 78.62; H, 8.40; N, 4.06.

Compound 6b. Yield: 72%; mp liquid. IR (KBr): 3060, 3030, 2930, 2850, 1620, 1600, 1570, 1490, 1450, 1370, 1330, 1270, 1210, 1150, 1080, 990, 810, 750, 700 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.87 (t, 3H, J = 6.2 Hz), 1.21 – 1.32 (m, 14H), 1.57 – 1.67 (m, 2H), 2.55 (t, 2H, J = 7.6 Hz), 2.66 (t, 2H, J = 7.6 Hz), 3.47 (t, 2H, J = 7.2 Hz), 3.88 (s, 3H), 4.97 (s, 2H), 6.80 (d, 1H, J = 8.5 Hz), 7.24 (d, 1H, J = 8.5 Hz), 7.28 – 7.35 (m, 3H), 7.39 ppm (d, 2H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$): δ 14.1, 20.2, 22.7, 27.4, 29.3, 29.4, 29.5, 29.6, 31.9, 36.1, 46.4, 55.6, 60.3, 74.7, 109.3, 121.9, 123.0, 128.1, 128.4, 132.5, 137.4, 143.7, 154.3, 167.1 ppm; HRMS Calcd. for $C_{27}H_{37}NO_2$: 407.2824; Found: 407.2829. *Anal.* Calcd. for $C_{27}H_{37}NO_2$: C, 79.56; H, 9.15; N, 3.44. Found: C, 79.61; H, 9.21; N, 3.50.

1-Alkyl-6-methoxy-3, 4-dihydroisoquinolin-5-ol (7). A solution of compound **6** (28.5 mmol), Pd/C (0.5 g) and methanol (150 mL) was stirred for 4 – 8 hours under a hydrogen atmosphere (using toy balloon) at room temperature. After filtering using Celite -545 pad, the filtrate was evaporated under reduced pressure. The resulting residue was applied to the top of an open-bed silica gel column (3.5 x 14 cm). The column was eluted with ethyl acetate. Fractions containing the product were combined and evaporated under reduced pressure to give the corresponding phenol **7**.

Compound 7a. Yield 85%; mp 115 - 116°C. IR (KBr): 3500, 3080, 2950, 2920, 2850, 1620, 1590, 1500, 1460, 1430, 1290, 1240, 1070, 870, 790 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.84 (t, 3H, J = 6.8 Hz), 1.23 – 1.36 (m, 6H), 1.55 – 1.65 (m, 2H), 2.67 – 2.76 (m, 4H), 3.62 (t, 2H, J = 7.4 Hz), 3.87 (s, 3H), 6.74 (d, 1H, J = 8.4 Hz), 7.06 (d, 1H, J = 8.4 Hz), 7.25 ppm (bs, 1H, D_2O exchangeable); ^{13}C NMR ($CDCl_3$): δ 14.1, 19.5, 22.6, 27.8, 29.3, 31.6, 35.9, 46.0, 55.7, 107.9, 117.6, 122.8, 124.6, 142.3, 149.0, 168.0 ppm. *Anal.* Calcd. for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.60; H, 8.91; N, 5.50.

Compound 7b. Yield: 70%; mp 108 – 109 °C. IR (KBr): 3450, 3010, 2930, 2850, 1640, 1610, 1570, 1490, 1460, 1440, 1290, 1240, 1150, 1080, 910, 740 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.86 (t, 3H, J = 6.3 Hz), 1.19 – 1.34 (m, 12H), 1.42 – 1.51 (m, 2H), 1.73 – 1.81 (m, 2H), 3.08 (t, 2H, J = 6.9 Hz), 3.20 (t, 2H, J = 7.3 Hz), 3.83 (t, 2H, J = 6.7Hz), 4.05 (s, 3H), 6.97 (d, 1H, J = 8.6 Hz), 7.43 (d, 1H, J = 8.6 Hz), 8.04 ppm (bs, 1H, D_2O exchangeable); ^{13}C NMR ($CDCl_3$): δ 14.0, 19.0, 22.6, 29.0, 29.1, 29.2, 29.3, 29.4, 29.5, 31.7, 32.7, 40.6, 56.5, 109.5, 117.8, 123.1, 123.6, 143.2, 154.3, 177.6 ppm. *Anal.* Calcd. for $C_{20}H_{31}NO_2$: C, 75.67; H, 9.84; N, 4.41. Found: C, 75.73; H, 9.90; N, 4.48.

1-Alkyl-5-arylalkoxy-6-methoxy-3,4-dihydroisoquinoline (8). A solution of compound **7** (11.5 mmol), potassium carbonate (13.8 mmol, 1.2 equiv), arylalkyl halide (16.1 mmol, 1.4 equiv) and methanol was refluxed until compound **7** was disappeared. After cooling to room temperature, the mixture was filtered. The filtrate was evaporated under reduced pressure. The resulting residue was applied to the top of an open-bed silica gel column. The column was eluted with ethyl acetate. Fractions containing the product were combined and evaporated under reduced pressure to give the product **8**.

Compound 8a. Yield 75%; mp 87 - 88°C. IR (KBr): 3050, 3010, 2950, 2920, 2850, 1630, 1600, 1570, 1490, 1450, 1430, 1370, 1330, 1270, 1220, 1140, 1080, 1050, 1040, 990, 820, 780, 730 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.88 (t, 3H, J = 6.5 Hz), 1.30 – 1.40 (m, 6H), 1.59 – 1.69 (m, 2H), 2.66 – 2.75 (m, 4H), 3.57 (t, 2H, J = 7.1 Hz), 3.87 (s, 3H), 5.30 (s, 2H), 6.82 (d, 1H, J = 8.5 Hz), 7.28 (d, 1H, J = 8.5 Hz), 7.51 (t, 1H, J = 7.4 Hz), 7.70 (t, 1H, J = 7.1 Hz), 7.81 (d, 1H, J = 8.1 Hz), 7.85 (d, 1H, J = 8.5 Hz), 8.06 (d, 1H, J = 8.4 Hz), 8.20 ppm (d, 1H, J = 8.5 Hz); ^{13}C NMR ($CDCl_3$): δ 14.1, 20.2, 22.6, 27.4, 29.3, 31.7, 36.1, 46.4, 55.6, 75.9, 109.4, 119.7, 122.1, 123.0, 126.4, 127.5, 127.6, 129.0, 129.6, 132.0, 136.7, 143.9, 147.4, 154.1, 158.3, 167.1 ppm; HRMS Calcd. for $C_{26}H_{30}N_2O_2$: 402.2307; Found: 402.2298. *Anal.* calcd. for $C_{26}H_{30}N_2O_2$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.62; H, 7.57; N, 7.02.

Compound 8b. Yield: 76%; mp oil. IR (KBr): 3090, 3030, 2920, 2850, 1620, 1600, 1570, 1490, 1450, 1370, 1330, 1280, 1220, 1150, 1080, 1000, 940, 870, 800, 710, 670 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.61, (t, 3H, J = 6.2 Hz), 0.98 – 1.11 (m, 6H), 1.32 –

1.38 (m, 2H), 2.33 (t, 2H, J = 7.3 Hz), 2.43 (t, 2H, J = 7.0 Hz), 3.25 (t, 2H, J = 7.5 Hz), 3.63 (s, 3H), 6.57 – 6.61 (m, 1H), 6.99 – 7.04 (m, 2H), 7.51 (d, 1H, J = 7.8 Hz), 8.27 – 8.29 Hz (m, 1H), 8.39 ppm (s, 1H); ^{13}C NMR ($CDCl_3$): δ 13.9, 19.9, 22.3, 25.2, 27.3, 28.8, 28.9, 31.2, 31.4, 35.2, 35.4, 45.5, 55.4, 71.7, 109.3, 122.4, 123.2, 131.8, 132.8, 135.9, 143.0, 148.0, 149.0, 149.2, 154.2, 167.4 ppm; HRMS Calcd. for $C_{22}H_{28}N_2O_2$: 352.2151; Found: 352.2147. *Anal.* calcd. for $C_{22}H_{28}N_2O_2$: C, 74.97; H, 8.01; N, 7.95. Found: C, 75.02; H, 8.04; N, 7.98.

Compound 8c. Yield: 62%; mp oil. IR (KBr): 3070, 3050, 2950, 2930, 2860, 2650, 1620, 1600, 1570, 1490, 1460, 1400, 1370, 1280, 1210, 1080, 1010, 830, 800, 740 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.87 (t, 3H, J = 6.7 Hz), 1.20 – 1.35 (m, 6H), 1.53 – 1.61 (m, 2H), 2.54 (t, 2H, J = 7.5 Hz), 2.64 (t, 2H, J = 7.6 Hz), 3.44 (t, 2H, J = 7.1 Hz), 3.85 (s, 3H), 4.90 (s, 2H), 6.79 (d, 1H, J = 8.6 Hz), 7.26 (d, 2H, J = 8.3 Hz), 7.38 (d, 1H, J = 8.3 Hz), 7.43 ppm (d, 2H, J = 8.6 Hz); ^{13}C NMR ($CDCl_3$): δ 14.1, 20.2, 22.5, 22.6, 27.4, 29.3, 31.7, 36.0, 46.3, 55.7, 73.8, 109.4, 122.0, 122.1, 122.9, 129.9, 131.5, 132.2, 136.5, 143.5, 154.2, 167.2 ppm; HRMS Calcd. for $C_{23}H_{28}BrNO_2$: 429.1303; Found: 429.1299. *Anal.* calcd. for $C_{23}H_{28}BrNO_2$: C, 64.19; H, 6.56; N, 3.25. Found: C, 64.21; H, 6.60; N, 3.32.

Compound 8d. Yield: 71%; mp 85 - 86°C. IR (KBr): 3090, 3070, 3030, 3000, 2950, 2930, 2890, 2840, 1620, 1600, 1570, 1520, 1490, 1450, 1350, 1270, 1210, 1140, 1080, 990, 850, 810 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.88 (t, 3H, J = 6.9 Hz), 1.27 – 1.40 (m, 6H), 1.59 – 1.68 (m, 2H), 2.63 – 2.71 (m, 4H), 3.56 (t, 2H, J = 7.1 Hz), 3.92 (s, 3H), 5.10 (s, 2H), 6.87 (d, 1H, J = 8.5 Hz), 7.31 (d, 2H, J = 8.5 Hz), 7.64 (d, 2H, J = 8.5 Hz), 8.21 (d, 2H, J = 8.6 Hz); ^{13}C NMR ($CDCl_3$): δ 14.0, 20.1, 22.5, 27.3, 29.2, 31.6, 36.0, 46.3, 55.7, 73.1, 109.4, 122.3, 123.0, 123.5, 131.9, 143.3, 145.1, 147.4, 153.9, 166.9 ppm; HRMS Calcd. for $C_{23}H_{28}N_2O_4$: 396.2049; Found: 396.2056. *Anal.* calcd. for $C_{23}H_{28}N_2O_4$: C, 69.67; H, 7.12; N, 7.07. Found: C, 69.70; H, 7.22; N, 7.11.

Compound 8e. Yield: 63%; mp oil. IR (KBr): 3060, 2930, 2850, 1770, 1710, 1620, 1600, 1570, 1490, 1430, 1390, 1270, 1220, 1080, 1020, 910, 740, 720 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.86 (t, 3H, J = 6.6 Hz), 1.23 – 1.36 (m, 6H), 1.54 – 1.62 (m, 2H), 2.57 – 2.65 (m, 4H), 3.49 (t, 2H, J = 7.1 Hz), 3.65 (s, 3H), 4.07 – 4.12 (m, 2H), 4.20 (t, 2H, J = 5.3 Hz), 6.71 (d, 1H, J = 8.5 Hz), 7.19 (d, 1H, J = 8.5 Hz), 7.71 – 7.75 (m, 2H), 7.85 - 7.88 ppm (m, 2H); ^{13}C NMR ($CDCl_3$): δ 14.0, 19.8, 22.5, 27.3, 29.2, 31.6, 36.0, 38.2, 46.2, 55.4, 69.4, 109.2, 121.9, 122.7, 123.2, 131.7, 132.1, 133.9, 143.7, 153.7, 167.0, 168.2 ppm; HRMS Calcd. for $C_{26}H_{30}N_2O_4$: 434.2206; Found: 434.2206. *Anal.* calcd. for $C_{26}H_{30}N_2O_4$: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.91; H, 7.02; N, 6.50.

Compound 8f. Yield: 77%; mp oil. IR (KBr): 3050, 2920, 2850, 1620, 1600, 1500, 1460, 1330, 1280, 1230, 1090, 880, 830, 790, 740 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.88 (t, 3H, J = 6.9 Hz), 1.16 – 1.30 (m, 14H), 1.46 – 1.62 (m, 3H), 1.79 – 1.89 (m, 1H), 2.57 – 2.63 (m, 1H), 2.85 – 3.00 (m, 2H), 3.18 -3.25 (m, 1H), 3.58 (s, 3H), 4.06 (s, 2H), 6.47 (d, 1H, J = 8.3 Hz), 6.59 (d, 1H, J = 8.3 Hz), 7.41 (t, 1H, J = 7.7 Hz), 7.59 (t, 1H, J = 7.1 Hz), 7.71 (d, 1H, J = 8.1 Hz), 7.79 (d, 1H, J = 8.5 Hz), 8.06 (d, 1H, J = 8.5 Hz), 8.14 ppm (d, 1H, J = 8.5 Hz); ^{13}C NMR ($CDCl_3$): δ 14.2, 18.6, 20.9, 22.8, 26.7, 29.5, 29.7, 29.8, 32.0, 36.6, 55.6, 60.1, 60.3, 61.1, 108.5, 118.2, 121.3, 121.6, 126.0, 127.4, 127.5, 129.0, 129.2, 132.1, 136.2, 143.2, 144.4, 147.4, 161.5, 170.9 ppm; HRMS Calcd. for $C_{30}H_{38}N_2O_2$: 458.2933; Found: 458.2930. *Anal.* calcd. for $C_{30}H_{38}N_2O_2$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.61; H, 8.39; N, 6.17.

Compound 8g. Yield: 83%; mp oil. IR (KBr): 3070, 3030, 2950, 2850, 1620, 1600, 1570, 1490, 1460, 1370, 1330, 1270, 1210, 1080, 1000, 800, 740, 710 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.87 (t, 3H, J = 6.9 Hz), 1.25 – 1.33 (m, 14H), 1.58 – 1.67 (m, 2H), 2.57 (t, 2H, J = 7.2 Hz), 2.67 (t, 2H, J = 7.5 Hz), 3.50 (t, 2H, J = 6.9 Hz), 3.89 (s, 3H), 5.00 (s, 2H), 6.83 (d, 1H, J = 8.4 Hz), 7.26 – 7.29 (m, 2H), 7.76 (d, 1H, J = 7.5 Hz), 8.54 (d, 1H, J = 8.4 Hz), 8. 64 ppm (s,1H); ^{13}C NMR ($CDCl_3$): δ 14.0, 20.0, 22.5, 27.2, 29.1, 29.2, 29.3, 29.4, 29.5, 31.7, 35.8, 46.1, 55.5, 71.8, 109.3, 122.1, 122.8, 123.2, 131.9, 132.9, 135.8, 143.1, 149.2, 149.4, 153.9, 166.9 ppm; HRMS Calcd. for $C_{26}H_{36}N_2O_2$: 408.2777; Found: 408.2785. *Anal.* calcd. for $C_{26}H_{36}N_2O_2$: C, 76.43; H, 8.88; N, 6.86. Found: C, 76.51; H, 8.90; N, 6.95.

Compound 8h. Yield: 80%; mp 51 – 52°C. IR (KBr): 3050, 2960, 2930, 1740, 1600, 1490, 1440, 1460, 1410, 1360, 1330, 1280, 1210, 1130, 1090, 1020, 840, 800, 740 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.85 (t, 3H, J = 6.9 Hz), 1.24 – 1.37 (m, 14H), 1.56 – 1.65 (m, 2H), 2.56 (t, 2H, J = 7.1 Hz), 2.65 (t, 2H, J = 7.4 Hz), 3.50 (t, 2H, J = 7.0 Hz), 3.87 (s, 3H), 4.91 (s, 2H), 6.79 (d, 1H, J = 8.5 Hz), 7.24 (d, 1H, J = 8.5 Hz), 7.26 – 7.34 ppm (m, 4H); ^{13}C NMR ($CDCl_3$): δ 14.1, 20.2, 22.7, 27.4, 29.3, 29.4, 29.5, 29.6, 29.7, 31.9, 36.1, 46.4, 55.6, 73.7, 109.3, 122.0, 123.0, 128.5, 129.6, 132.3, 133.8, 136.0, 143.5, 154.1, 167.0 ppm; HRMS Calcd. for $C_{27}H_{36}ClNO_2$: 441.2435; Found: 441.2435. *Anal.* calcd. for $C_{27}H_{36}ClNO_2$: C, 73.36; H, 8.21; N, 3.17. Found: C, 73.41; H, 8.42; N, 3.21.

Compound 8i. Yield: 59%; mp 80 – 81°C. IR (KBr): 3080, 3030, 2950, 2920, 2850, 1770, 1710, 1630, 1600, 1490, 1460, 1430, 1400, 1320, 1270, 1200, 1080, 1050, 1020, 990, 720 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.86 (t, 3H, J = 6.9 Hz), 1.24 – 1.35 (m, 14H), 1.54 – 1.63 (m, 2H), 2.57 – 2.65(m, 4H), 3.50 (t, 2H, J = 7.1 Hz), 3.64 (s, 3H), 4.08 (t, 2H, J = 5.5 Hz), 4.20 (t, 2H, J = 5.3 Hz), 6.70 (d, 1H, J = 8.5 Hz), 7.19 (d, 1H, J = 8.5 Hz), 7.75 – 7.69 (m, 2H), 7.83 – 7.87 ppm (m, 2H); ^{13}C NMR ($CDCl_3$): δ 14.1, 19.8, 22.6, 27.3, 29.3, 29.4, 29.5, 29.6, 29.7, 31.8, 36.0, 38.2, 46.2, 55.3, 69.4, 109.2, 121.8, 122.7, 123.1, 131.7, 132.1, 133.9, 143.7, 153.7, 167.0, 168.1 ppm; HRMS Calcd. for $C_{30}H_{38}N_2O_4$: 490.2832; Found: 490.2828. *Anal.* calcd. for $C_{30}H_{38}N_2O_4$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.49; H, 7.93; N, 5.76.

Compound 8j. Yield: 91%; mp oil. IR (KBr): 3060, 2930, 2850, 1770, 1710, 1620, 1600, 1570, 1490, 1440, 1400, 1370, 1340, 1270, 1220, 1080, 1050, 940, 900, 800, 720 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.87 (t, 3H, J = 6.9 Hz), 1.29 – 1.41 (m, 14H), 1.59 – 1.69 (m, 2H),1.80 – 1.98 (m, 4H), 2.64 – 2.71(m, 4H), 3.58 (t, 2H, J = 7.4 Hz), 3.78 (t, 2H, J = 7.1 Hz), 3.88 (s, 3H), 3.95 (t, 2H, J = 5.9 Hz), 6.79 (d, 1H, J = 8.5 Hz), 7.24 (d, 1H, J = 8.5 Hz), 7.69 – 7.72 (m, 2H), 7.81 – 7.84 ppm (m, 2H); ^{13}C NMR ($CDCl_3$): δ 14.1, 19.9, 20.9, 22.6, 25.3, 27.4, 27.6, 29.2, 29.3, 29.4, 31.8, 36.0, 37.6, 46.4, 55.5, 60.2, 72.1, 109.2, 121.7, 122.9, 123.0, 132.0, 132.1, 133.8, 144.0, 154.2, 167.1, 168.3, 170.9 ppm; HRMS Calcd. for $C_{32}H_{42}N_2O_4$: 518.3145; Found: 518.3142. *Anal.* calcd. for $C_{32}H_{42}N_2O_4$: C, 74.10; H, 8.16; N, 5.40. Found: C, 74.18; H, 8.21; N, 5.47.

Compound 8k. Yield: 71%; mp 92 – 93 °C. IR (KBr): 3070, 2920, 2850, 1670, 1610, 1570, 1490, 1450, 1390, 1280, 1210, 1080, 860, 750 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.88 (t, 3H, J = 5.6 Hz), 1.26 – 1.36 (m, 14H), 1.58 – 1.67 (m, 2H), 2.64 (t, 2H, J = 7.5 Hz), 2.72 (t, 2H, J = 7.5 Hz), 3.65 (t, 2H, J = 7.2 Hz), 3.87 (s, 3H), 5.85 (s, 2H), 6.94 (d, 1H, J = 8.6 Hz), 7.34 (s, 1H), 7.49 ppm (d, 1H, J = 8.6 Hz); ^{13}C NMR ($CDCl_3$): δ 14.1, 19.7, 22.7, 27.2, 29.3, 29.4, 29.5, 29.6, 29.7, 31.9, 36.0, 45.7, 56.2, 58.3,

109.8, 117.2, 123.2, 124.9, 129.9, 131.8, 137.5, 152.4, 153.9, 157.8, 166.4 ppm; HRMS Calcd. for $C_{25}H_{33}Cl_2N_3O_3$: 493.1899; Found: 493.1899. *Anal.* calcd. for $C_{25}H_{33}Cl_2N_3O_3$: C, 60.73; H, 6.73; N, 8.50. Found: C, 60.76; H, 6.80; N, 8.56.

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