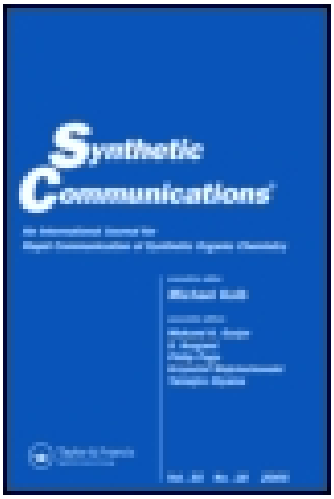

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EFFICIENT SYNTHESES OF (±)-CHERYLLINE AND LATIFINE DIMETHYL ETHER

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A concise route for the syntheses of (±)-cherylline and latifine dimethyl ether is reported. The key steps involved are Michael addition of veratrole with p-methoxy nitrostyrene (for cherylline), anisole with 2,3-dimethoxy nitrostyrene (for latifine), and reduction of nitro intermediate, followed by Pictet–Spengler cyclization.

Keywords: Michael reaction; Pictet–Spengler cyclization; reduction; tetrahydroisoquinolines

INTRODUCTION

Cherylline (**1**) and latifine (**2**) are the two 4-aryltetrahydroisoquinoline alkaloids isolated from *Amaryllidaceae* plants. 4-Aryltetrahydroisoquinolines are of interest because of their various pharmacological activities.[1] For example, nomifensine **3** and dichlorofensine[2] **4** exhibit central nervous system activity and inhibit serotonin and dopamine uptake mechanisms (Fig. 1).

There are several reports of the syntheses of (±)-cherylline[3–11] and (±)-latifine,[12–15] which include some efficient chiral syntheses. Most of the reported methods for the synthesis of (±)-cherylline are multistep. We report herein an alternative efficient synthesis of (±)-cherylline dimethyl ether. The key steps involved are Michael addition of veratrole with p-methoxy nitrostyrene, reduction of the nitro intermediate, and then the Pictet–Spengler cyclization.

RESULTS AND DISCUSSION

Our retrosynthetic analysis of (±)-cherylline dimethyl ether **5** or latifine dimethyl ether **6** is depicted in Scheme 1. We anticipated that **5** and **6** could be constructed from amine **7** and **8** via a Pictet–Spengler ring annulation, which, in turn, could be obtained by reduction of the corresponding nitro intermediates **9**

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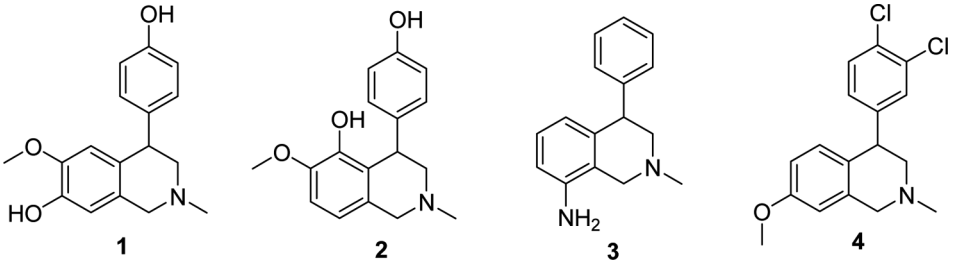
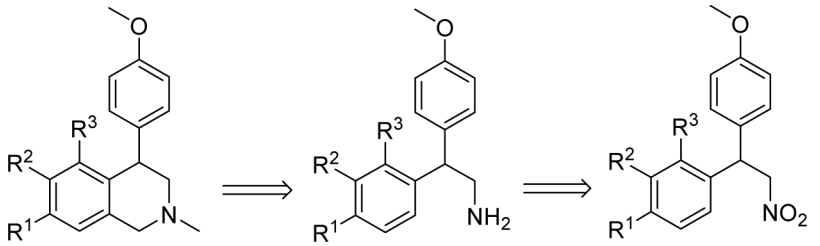


Figure 1. Aryl-1,2,3,4-tetrahydroisoquinolines.

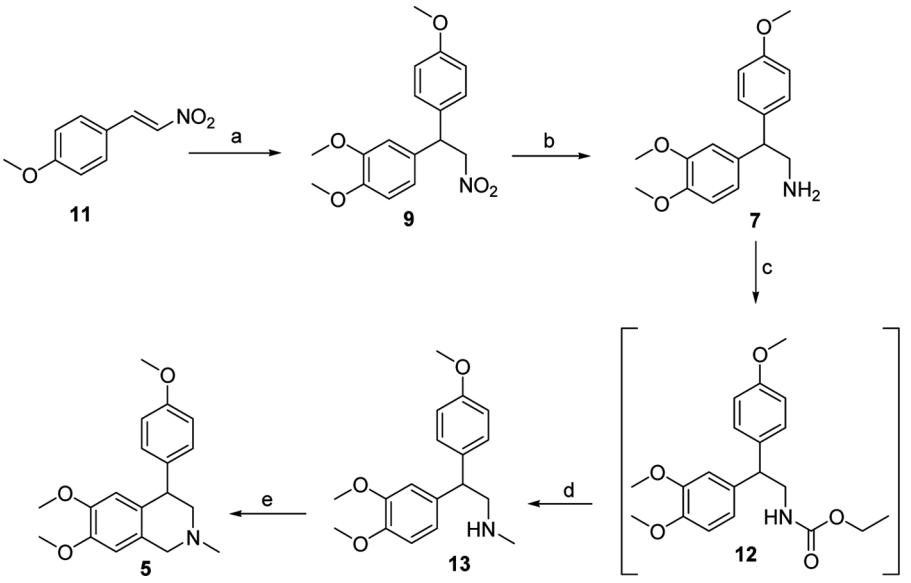
and **10**. The required nitro intermediates would arise from the Michael addition of veratrole with p-methoxy nitrostyrene (for cherylline) and anisole with 2,3-dimethoxy nitrostyrene (for latifine).

For cherylline dimethyl ether, veratrole was subjected to Michael reaction with p-methoxy nitrostyrene **11** in the presence of trifluoroacetic acid (TFA) to obtain 1-(1-(3,4-dimethoxyphenyl)-2-nitroethyl)-4-methoxybenzene **9** in 90% yield. Reduction of nitro group with iron under acidic conditions in tetrahydrofuran (THF) at room temperature gave 2-(3,4-dimethoxyphenyl)-2-(4-methoxyphenyl) ethanamine **7** in 74% yield. Reaction with ethyl chloroformate using trimethylamine at room temperature gave ethyl 2-(3,4-dimethoxyphenyl)-2-(4-methoxyphenyl) ethyl-carbamate intermediate **12**, and immediate reduction by lithium aluminium hydride gave N-methyl amine **13** in 90% yield. The crude amine **13**, after the Pictet–Spengler reaction, gave (±)-cherylline dimethyl ether **5** in 60% yield (Scheme 2).

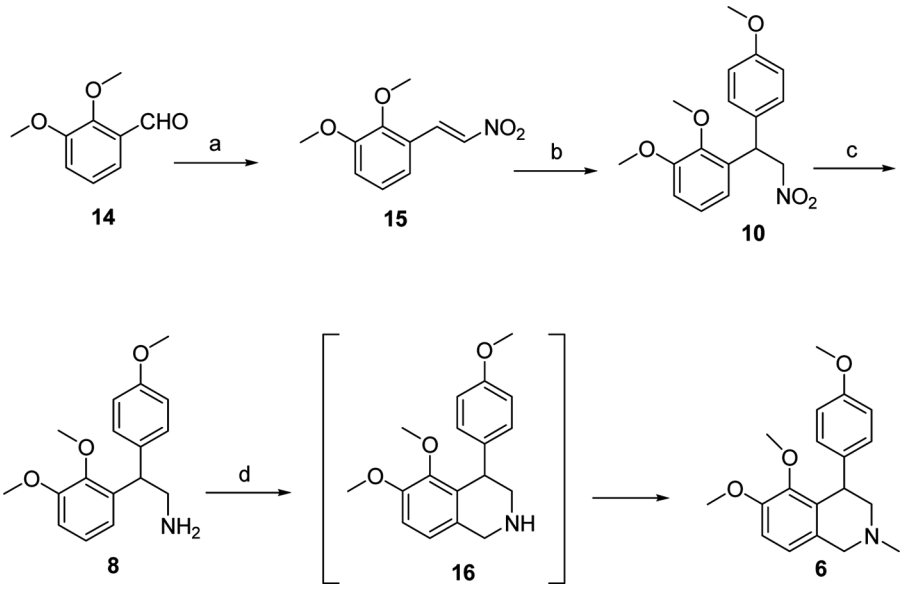
For latifine dimethyl ether, anisole was subjected to Michael reaction with 2,3-dimethoxy nitrostyrene **15** in presence of TFA to obtain 1-(1-(2,3-dimethoxyphenyl)-2-nitroethyl)-4-methoxybenzene **10** in 50% yield. Reduction of the nitro group with iron under acidic conditions in THF gave 2-(2,3-dimethoxyphenyl)-2-(4-methoxyphenyl)ethanamine **8** in 80% yield. The crude amine **8**, after Pictet–Spengler reaction, gave (±)-latifine dimethyl ether **6** in 60% yield (Scheme 3). A mixture of **8** with formaldehyde and formic acid for 2 h at reflux undergoes the Pictet–Spengler reaction and reductive N-methylation reaction in a single step to provide (±)-latifine dimethyl ether **6** in 60% yield. The key steps in latifine synthesis was conversion of 2-(2,3-dimethoxyphenyl)-2-(4-methoxyphenyl) ethanamine **8** to (±)-latifine dimethyl ether **6** in a single step using excess equivalents



Scheme 1. 5: $R^1 = R^2 = OMe$, $R^3 = H$ 6: $R^2 = R^3 = OMe$, $R^1 = H$ 7: $R^1 = R^2 = OMe$, $R^3 = H$ 8: $R^2 = R^3 = OMe$, $R^1 = H$ 9: $R^1 = R^2 = OMe$, $R^3 = H$ 10: $R^2 = R^3 = OMe$, $R^1 = H$.



Scheme 2. (a) Veratrole, TFA, reflux, 3.0 h, 90.0%; (b) Fe, acetic acid, THF, 70 °C, 3.0 h, 74%; (c) ethyl chloro formate, TEA, THF, 0–5 °C; (d) LAH, THF, reflux, 4.0 h, 90%; and (e) HCHO, acetic acid, 90 °C, 2.0 h, 60%.



Scheme 3. (a) Nitromethane, CH_3COONH_4, acetic acid, 100 °C, 4.0 h, 60%; (b) anisole, TFA, reflux, 3.0 h, 50%; (c) Fe, acetic acid, THF, 70 °C, 3.0 h, 80%; and (d) HCHO, HCOOH, 90 °C, 2.0 h, 60%.

of aqueous formaldehyde and formic acid. The initial reaction undergoes Pictet–Spengler cyclization to produce 5,6-dimethoxy-4-(4-methoxyphenyl)-1,2,3,4-tetrahydro isoquinoline **16** (without isolation) and then reductive N-methylation reaction in a single step to produce the desired product in good yield.

In short, we have devised a short and efficient method for the syntheses of (±)-cherylline and latifine dimethyl ethers. This simple and facile nature of tetrahydroisoquinoline synthesis should allow the construction of a wide variety of interesting and useful analogous molecules.

EXPERIMENTAL

Materials and Instruments

All solvents and reagents were purchased from the suppliers and used without further purification. All nonaqueous reactions were performed in dry glassware under an atmosphere of dry nitrogen. Organic solutions were concentrated under reduced pressure. Thin-layer chromatography (TLC) was performed on Merck precoated silica-gel $60F_{254}$ plates. ^1H and ^{13}C NMR spectra were recorded in dimethylsulfoxide (DMSO-d_6) and $CDCl_3$ on a Varian Gemini 400-MHz Fourier transform (FT) NMR spectrometer. The chemical shifts are reported in δ ppm relative to tetramethylsilane (TMS). The infrared (IR) spectra were recorded in the solid state as KBr dispersion using a Perkin Elmer FT-IR spectrophotometer. The mass spectra were recorded on a Shimadzu liquid chromatography–mass spectrometer (LCMS) QP 800 and AB-4000 Q-trap LC-MS/MS instruments. Melting points were obtained by using the open capillary method and are uncorrected.

1-(1-(3,4-Dimethoxyphenyl)-2-nitroethyl)-4-methoxybenzene (9)

A solution of p-methoxy nitrostyrene **11** (6.0 g, 0.033 mol) and veratrole (9.2 g, 0.067 mol) in TFA (30 mL) was refluxed for 3 h. TFA was distilled under pressure, and saturated $NaHCO_3$ (50 mL) was added. It was extracted with ethyl acetate (3×30 ml), and combined extracts were dried over sodium sulfate and concentrated. The residue was purified by column chromatography on silica gel (7:3 hexane and ethyl acetate) to yield **9** as a residue (9.6 g, 90%); IR (KBr, cm^{-1}): 1550 (NO_2); ^1H NMR (DMSO-d_6) (δ ppm): 3.62 (3H, s, $-OCH_3$), 3.64 (3H, s, $-OCH_3$), 3.66 (3H, s, $-OCH_3$), 4.63 (1H, t, $J = 8.8$ Hz, Ar-CH-Ar), 5.21 (2H, d, $J = 8.8$ Hz, CH_2-NO_2), 6.77–7.27 (7H, m, ArH); ^{13}C NMR (DMSO-d_6) (δ ppm); 47.8 (ArCHAr), 55.4 (OCH_3), 55.8 (OCH_3), 55.9 (OCH_3), 79.1 (CH_2-NO_2), 111.9 (CH_{ar}), 112.2 (CH_{ar}), 114.3 ($2 \times CH_{ar}$), 119.8 (C_{ar}), 129.0 ($2 \times CH_{ar}$), 132.8 (C_{ar}), 133.3 (C_{ar}), 148.1 (OC_{ar}), 149.1 (OC_{ar}), 158.5 (OC_{ar}); MS (m/z): 318 [$M^+ + 1$].

The 2,3-dimethoxy congener (**10**) was obtained in the same way as an oil (50%); IR (KBr, cm^{-1}): 1550 (NO_2); HRMS m/z calculated for $C_{17}H_{19}NO_5$ 318.1263-[M + 1], found 318.1260; ^1H NMR (400 MHz, DMSO-d_6) (δ ppm): 3.72 (3H, s, $-OCH_3$), 3.74 (3H, s, $-OCH_3$), 3.86 (3H, s, $-OCH_3$), 4.65 (1H, t, $J = 8.8$ Hz, Ar-CH-Ar), 5.19 (2H, d, $J = 8.8$ Hz, CH_2-NO_2), 6.78–6.98 (5H, m, ArH), 7.21 (2H, d, $J = 8.0$ Hz, ArH); ^{13}C NMR (400 MHz, DMSO-d_6) (δ ppm); 46.8 (ArCHAr), 55.4 (OCH_3), 55.8 (OCH_3), 60.5 (OCH_3), 79.2 (CH_2-NO_2), 111.6 (CH_{ar}), 114.4

($2 \times CH_{ar}$), 120.3 (CH_{ar}), 121.9 (CH_{ar}), 129.1 ($2 \times CH_{ar}$), 131.9 (C_{ar}), 132.7 (C_{ar}), 147.8 (OC_{ar}), 152.4 (OC_{ar}), 157.2 (OC_{ar}).

2-(3,4-Dimethoxyphenyl)-2-(4-methoxyphenyl)ethanamine (7)

Iron (10.5 g, 0.189 mol) was added to a solution of 1-(1-(3,4-dimethoxy phenyl)-2-nitroethyl)-4-methoxybenzene **9** (6.0 g, 0.018 mol) in THF (60 mL) and acetic acid (60 mL). The reaction mixture stirred at reflux for 3 h. After cooling to room temperature, the reaction mixture was filtered through a celite bed and basified with 50% sodium hydroxide solution. This basified solution was extracted ethyl acetate (3×25 mL), dried, filtered, and concentrated to obtain 5.3 g of crude product. Purification of crude product by column chromatography using 10% methanol in dichloromethane as an eluent gave **7** (4.0 g, 74%), as a residue; IR (KBr, cm^{-1}): 3320 (NH_2); ^{1}H NMR (DMSO-d_6) (δ ppm): 3.03 (2H, d, $J = 7.8$ Hz, $-CH-CH_2-$), 3.62 (3H, s, $-OCH_3$), 3.63 (3H, s, $-OCH_3$), 3.65 (3H, s, $-OCH_3$), 3.73 (1H, t, $J = 7.8$ Hz, $CH-CH_2$), 6.68–7.11 (7H, m, ArH); ^{13}C NMR (DMSO-d_6) (δ ppm); 47.2 (ArCHAr), 53.7 (CH_2-NH_2), 55.3 (OCH_3), 55.8 (OCH_3), 55.9 (OCH_3), 112.2 (CH_{ar}), 112.3 (CH_{ar}), 114.1 ($2 \times CH_{ar}$), 119.9 (C_{ar}), 129.1 ($2 \times CH_{ar}$), 136.3 (C_{ar}), 136.8 (C_{ar}), 147.5 (OC_{ar}), 149.0 (OC_{ar}), 157.9 (OC_{ar}); MS (m/z): 288 [$M^+ + 1$].

The 2,3-dimethoxy congener (**8**) was obtained in the same way as an oil in 80%; IR (KBr, cm^{-1}): 3320 (NH_2); HRMS m/z calculated for $C_{17}H_{21}NO_3$ 288.1521 [M + 1], found 288.1522; ^{1}H NMR (400 MHz, DMSO-d_6) (δ ppm): 3.03 (2H, d, $J = 7.8$ Hz, $-CH_2-NH_2$), 3.54 (3H, s, $-OCH_3$), 3.66 (3H, s, $-OCH_3$), 3.72 (3H, s, $-OCH_3$), 4.21 (1H, t, $J = 7.8$ Hz, $CH-CH_2$), 6.78–6.98 (5H, m, ArH), 7.13 (2H, d, $J = 8.0$ Hz ArH); ^{13}C NMR (400 MHz, DMSO-d_6) (δ ppm); 47.2 (ArCHAr), 46.8 (CH_2-NH_2), 55.3 (OCH_3), 55.9 (OCH_3), 60.4 (OCH_3), 111.0 (CH_{ar}), 114.0 ($2 \times CH_{ar}$), 119.6 (CH_{ar}), 124.2 (CH_{ar}), 129.4 ($2 \times CH_{ar}$), 135.9 (C_{ar}), 137.5 (C_{ar}), 147.0 (OC_{ar}), 152.9 (OC_{ar}), 157.9 (OC_{ar}).

2-(3,4-Dimethoxyphenyl)-2-(4-methoxyphenyl)-N-methylethanamine (13)

Ethyl chloroformate (1.5 g, 0.013 mol) was added to a solution of 2-(3,4-dimethoxyphenyl)-2-(4-methoxyphenyl)ethanamine **7** (3.5 g, 0.012 mol) in THF (35 mL) and triethyl amine (1.85 g, 0.018 mol) at 0–5 °C. The reaction mixture stirred at 25–35 °C for 1 h. Reaction progress was monitored by TLC and shown to be pure; it proceeded as such for reduction purposes. Intermediate **12** (ethyl 2-(3,4-dimethoxyphenyl)-2-(4-methoxyphenyl)ethylcarbamate) was slowly added to the suspension of lithium aluminium hydride (LAH) (2.3 g, 0.06 mol) in THF (15 mL) under an inert atmosphere. After refluxing for 4 h, the reaction mixture was cooled to 5 °C, and chilled water was slowly added to it. The aluminium hydroxide formed was filtered over celite and washed with chloroform. The filtrate also was extracted with chloroform (3×20 mL). All the organic extracts and washings were combined, dried over sodium sulfate, filtered, and concentrated to obtain **13** as a brown residue 3.3 g (90.0%); IR (KBr, cm^{-1}): 3120 (NH); HRMS m/z calculated for $C_{18}H_{23}NO_3$ 302.3801 [M + 1], found 302.37; ^{1}H NMR ($CDCl_3$) (δ ppm): 2.44 (3H, s, NCH_3), 3.12 (2H, d, $J = 8.0$ Hz, $HCH-N-CH_3$), 3.78 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 4.08 (1H,

t, $J = 7.6$ Hz, Ar-CH-Ar), 6.74–7.26 (7H, m, ArH); ^{13}C NMR ($CDCl_3$) (δ ppm); 43.9 (NCH_3), 49.4 (ArCHAr), 55.3 (OCH_3), 55.81 (OCH_3), 55.86 (OCH_3), 56.6 (NCH_2Ar), 112.1 (CH_{ar}), 112.2 (CH_{ar}), 114.1 ($2 \times CH_{ar}$), 119.8 (C_{ar}), 129.0 ($2 \times CH_{ar}$), 136.2 (C_{ar}), 136.8 (C_{ar}), 147.5 (OC_{ar}), 148.9 (OC_{ar}), 157.9 (OC_{ar}).

(±)-Cherylline Dimethyl Ether (5)

A mixture of **13** (2.0 g, 0.006 mol), formaldehyde (0.64 g, 0.007 mol), and acetic acid (5 mL) was stirred at 90 °C under an inert atmosphere for 2.0 h. After cooling to room temperature, the reaction mixture was basified with saturated $NaHCO_3$ solution. This basified solution was extracted ethyl acetate (3×25 mL), dried, filtered, and concentrated to obtain 1.1 g of crude product. Purification of crude product by column chromatography using 1% methanol in dichloromethane as an eluent gave **5** (0.93 g, 45%), as a white solid, mp 90–92 °C (lit.[11] mp 90–92 °C); IR (KBr, cm^{-1}): 1610, 1514; HRMS m/z calculated for $C_{19}H_{23}NO_3$ 314.1756 [M + 1], found 314.175; ^{1}H NMR ($CDCl_3$) (δ ppm): 2.41 (3H, s, NCH_3), 2.44 (1H, m, CH−HCH−N), 2.98 (1H, m, CH−HCH−N), 3.56 (2H, s (br), Ar−CH_2−N), 3.65 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 4.12 (1H, t, Ar−CH−Ar), 6.34 (1H, s, 5-CH), 6.56 (1H, s, 8-CH), 6.84 (2H, d, $J = 8.8$ Hz, 2′-CH), 7.11 (2H, d, $J = 8.8$ Hz, 3′-CH); ^{13}C NMR ($CDCl_3$) (δ ppm); 43.9 (NCH_3), 45.9 (ArCHAr), 55.3 (OCH_3), 55.81 (OCH_3), 55.86 (OCH_3), 57.7 (NCH_2−), 61.6 (NCH_2Ar), 109.7 (CH_{ar}), 112.5 (CH_{ar}), 113.9 ($2 \times CH_{ar}$), 127.7 (C_{ar}), 129.2 (C_{ar}), 130.0 ($2 \times CH_{ar}$), 137.7 (C_{ar}), 147.5 (OC_{ar}), 147.6 (OC_{ar}), 158.0 (OC_{ar}).

(±)-Latifine Dimethyl Ether (6)

A mixture of **8** (2.0 g, 0.006 mol), formaldehyde 37% solution in water (2.81 g, 0.034 mol), and formic acid (6 mL) was stirred at 95 °C under an inert atmosphere for 18.0 h. After cooling to room temperature, the reaction mixture was basified with 50% sodium hydroxide solution. This basified solution was extracted ethyl acetate (3×25 mL), dried, filtered, and concentrated to obtain 0.9 g of crude product. Purification of crude product by column chromatography using 1% methanol in dichloromethane as an eluent gave **6** (1.30 g, 60%) as a white solid, mp 86–88 °C (lit.[16] mp 86–88 °C); IR (KBr, cm^{-1}): 1620, 1520; HRMS *m/z* calculated for $C_{19}H_{23}NO_3$ 314.1756 [M + 1], found 314.1758; ^{1}H NMR (400 MHz, $CDCl_3$) (δ ppm): 2.32 (3H, s, NCH_3), 2.70 (2H, d, $J = 4.4$ Hz, CH−CH_2−N), 3.20 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 3.34 and 3.80 (each 1H, d, $J = 14.4$ Hz, Ar-*HCH*−N), 4.26 (1H, t, $J = 4.4$ Hz, Ar−CH−Ar), 6.76–6.80 (4H, m, ArH), 7.11 (2H, d, $J = 8.8$ Hz, ArH); ^{13}C NMR (400 MHz, $CDCl_3$) (δ ppm); 40.5 (ArCHAr), 46.1 (NCH_3), 55.1 (OCH_3), 55.7 (OCH_3), 57.9 (NCH_2Ar), 59.4 (NCH_2), 61.5 (OCH_3), 111.1 (CH_{ar}), 113.1 ($2 \times CH_{ar}$), 121.1 (CH_{ar}), 128.7 (C_{ar}), 129.3 ($2 \times CH_{ar}$), 130.2 (C_{ar}), 139.9 (C_{ar}), 147.8 (OC_{ar}), 151.1 (OC_{ar}), 157.6 (OC_{ar}).

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