



New synthesis of 1-[(3,4-dimethoxyphenyl)methoxymethyl]-6,7-dimethoxyisoquinoline (setigerine), a naturally occurring alkaloid, and some derivatives of papaverine

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ABSTRACT

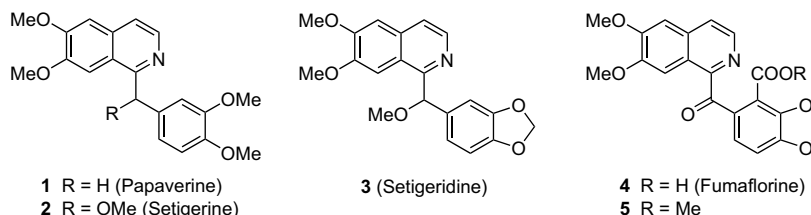
A novel and improved synthetic route for the preparation of the new alkaloid setigerine, isolated from *Papaver setigerum* DC, and some new 3,4-dihydropapaverine and papaverine derivatives is reported. This method is based on the side chain chlorination of 1-benzyl-3,4-dihydroisoquinolines using *N*-chloro-succinimide (NCS) and subsequent reaction with sodium methoxide in methanol to give the corresponding isoquinolines.

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1. Introduction

The isoquinoline nucleus is the core of an important family of alkaloids.¹ 1-Substituted isoquinolines are the most important members of this isoquinoline family, which are either naturally occurring alkaloids or intermediates in both organic synthesis and biosynthesis.² Examples include protoberberines, aporphines, and papaverines. These kinds of alkaloids have interesting biological activities and many of them have found a therapeutical use.³ In the past, several novel naturally occurring papaverine isoquinolines **2** (setigerine) and **3** (setigeridine) have been isolated from *Papaver setigerum* DC,⁴ while isoquinolines **4** (fumaflorine) and **5** were isolated from *Fumaria densiflora* DC.⁵

Since papaverine **1** and some of its derivatives are known to exhibit interesting biological activities, such as muscle relaxation,⁶ hepatotoxicity, and antimalarial activity,⁷ the modification of papaverine has been attractive in organic synthesis.⁸ In the past, the naturally occurring papaverine derivative setigerine **2** was synthesized by methylation of papaverinol with iodomethane in 18% yield.⁹ Recently, we identified 1-(1,1-dichloroalkyl)- and 1-(trichloromethyl)-3,4-dihydroisoquinoline to be suitable sources for the synthesis of functionalized isoquinolines. These promising results initiated us to develop a new convenient method for the synthesis of setigerine **2** and 3,4-dihydropapaverine derivatives from 1-(α,α -dichloroaryl)methyl-3,4-dihydroisoquinolines via a 1,4-dehydrochlorination protocol.



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2. Results and discussion

3,4-Dihydroisoquinolines **7a–c**¹⁰ were synthesized in 69–76% yield from *N*-2-arylethyl amides **6a,b** by the Bischler–Napieralski reaction involving a cyclocondensation with polyphosphoric acid in toluene under reflux for 3–10 h (Scheme 1). The cyclization of amide **6c** was performed with an excess of POCl₃ in boiling dichloromethane for 16 h, followed by treatment with a 40 wt% aqueous solution of sodium hydroxide to give 3,4-dihydroisoquinoline **7c** in 73% yield. Isoquinolines **7a–c** were treated with 2 equiv of *N*-chlorosuccinimide (NCS) in a 1:1 mixture of dichloromethane and carbon tetrachloride at room temperature for 1–4 h to give 1-(α,α -dichloroaryl-methyl)-3,4-dihydroisoquinolines **8a–c** in excellent yield (77–97%). These novel compounds **8a–c** decomposed rapidly upon contact with silica gel during column chromatography, therefore they were immediately used in the next step without purification.

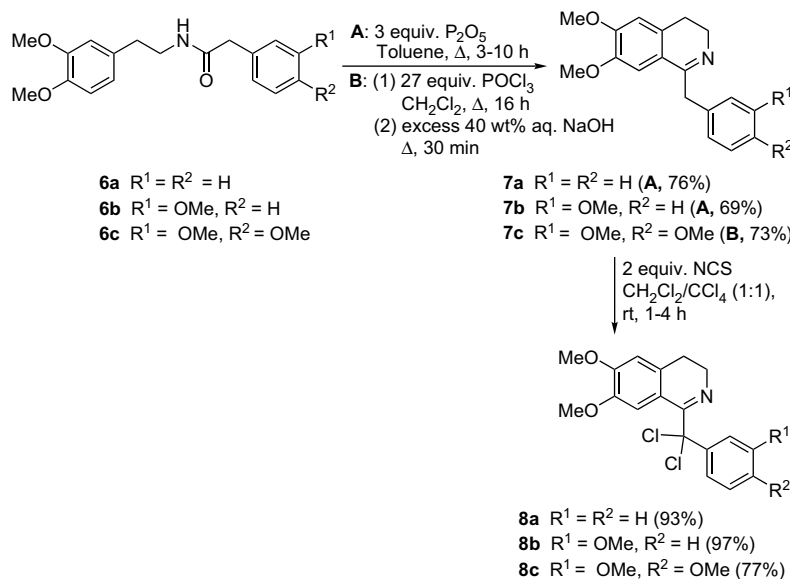
Since we found that 1-(α,α -dichloroalkyl)-3,4-dihydroisoquinolines can be conveniently converted into functionalized isoquinolines by treatment with different bases, this method was applied for the synthesis of the natural product setigerine **2**. In order to develop this method for the functionalization of 1-(aryldichloromethyl)-3,4-dihydroisoquinolines, compounds **8a,b** were treated with 5 equiv of a 2 M solution of sodium methoxide in methanol under reflux for 3 h. Under these reaction conditions, the isoquinoline derivatives **9a,b** were obtained in 60–81% yield and setigerine **2** was obtained in only 15% yield. In addition, some 1-(aryldimethoxymethyl)-3,4-dihydropapaverine derivatives **10a,b** were also obtained in 10–16% yield, and **10c** in 74% yield

(Scheme 2). The mechanism of the aromatization of 1-(alkyldichloromethyl)-3,4-dihydroisoquinolines **8** to isoquinolines **9** concerns a 1,4-dehydrochlorination, followed by tautomerization and subsequent nucleophilic substitution of the remaining chlorine by methoxide (Scheme 3). However, under the above mentioned reaction conditions substrates **8a–c** underwent also double nucleophilic substitution to iminoacetals **10a–c** in a competitive reaction.

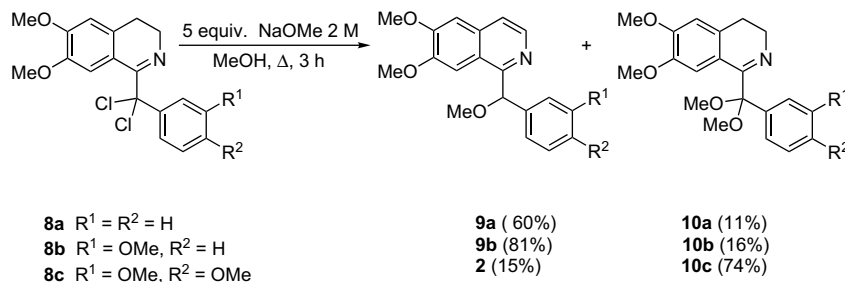
In order to increase the yield of setigerine **2**, 1-[dichloro-(3,4-dimethoxyphenyl)methyl]-3,4-dihydro-6,7-dimethoxyisoquinoline **8c** was reacted with 3 equiv of 5 M sodium methoxide in methanol under reflux for 3 h, resulting in the isolation of setigerine **2** in 60% yield. 3,4-Dihydroisoquinoline **10c** was also obtained in 10% yield, showing the pronounced tendency of such double benzylic and heteroallylic dichlorides **8c** to solvolyse (Scheme 4).

In order to underline the necessary role of the base in the aromatization reaction to isoquinolines **2** and **9a,b** and to prove the tendency of α,α -dichloroimines **8a–c** for methanolysis, 1-(aryldichloromethyl)-3,4-dihydroisoquinolines **8a,b** were treated with 2 equiv of triethylamine in boiling methanol for 3 h. Products **10a,b** were obtained in excellent yield (82–96%) (Scheme 5), proving the methanolysis tendency and the absence of aromatization products **9a,b**.

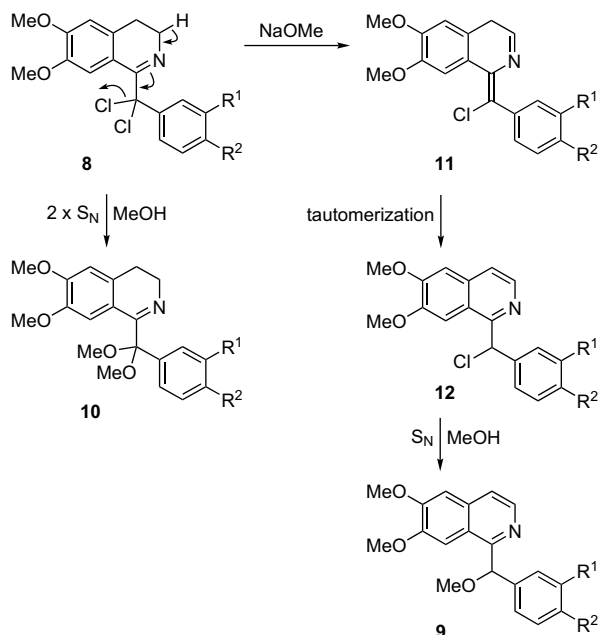
In conclusion, based on the Bischler–Napieralski reaction and subsequent dichlorination, several 3,4-dihydroisoquinolines **8a–c** were either converted into isoquinolines **9** or iminoacetals **10** depending on the concentration of sodium methoxide in methanol. This reaction was applied to an efficient synthesis of the isolated natural product setigerine **2**.



Scheme 1.



Scheme 2.



Scheme 3.

3. Experimental part

3.1. General

^1H NMR (270 MHz) and ^{13}C NMR (67 MHz) spectra were recorded with a Jeol JNM-EX 270 NMR spectrometer. IR spectra were measured with a Perkin Elmer model 983 spectrophotometer. Mass spectra were recorded with a Varian-MAT 112 mass spectrometer (70 eV). Melting points were measured with a Buchi 535 apparatus.

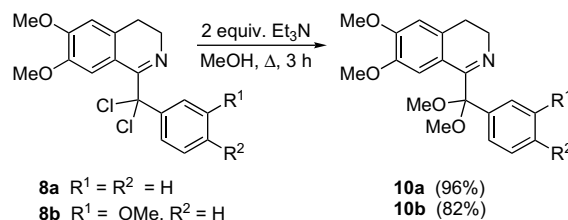
3.2. Synthesis of 1-(arylmethyl)-3,4-dihydro-6,7-dimethoxyisoquinolines **7a–c**

3.2.1. Procedure A

Polyphosphoric acid was obtained from 85% phosphoric acid and P_2O_5 (1:1 w/w). To a solution of 1.0 mmol of carboxylic amides **6a** and **6b** in 30 ml of toluene, 3 mmol of polyphosphoric acid was added dropwise. The reaction mixture was refluxed for 3–10 h. Then, this mixture was poured into ice water and extracted three times with CH_2Cl_2 . The combined extracts were washed with NaHCO_3 (5%), dried (MgSO_4), and evaporated in vacuo to give 3,4-dihydroisoquinolines **7a** and **7b** in 76% and 69% yield, respectively. The spectral data of 3,4-dihydroisoquinoline **7a** were in accordance with the literature.^{10a}

3.2.2. Procedure B

A solution of 1.0 g (2.8 mmol) of carboxylic amide **6c**^{10b} in 60 ml of CH_2Cl_2 was treated with an excess of POCl_3 (7.0 ml, 75.2 mmol) at reflux for 16 h. Then, a 40 wt % aqueous sodium hydroxide solution



Scheme 5.

was added cautiously until the pH of the aqueous phase was basic and the resulting mixture was boiled under reflux for 30 min. The reaction mixture was poured in water and extracted with dichloromethane. The combined extracts were washed with water, dried (MgSO_4), and evaporated in vacuo to give 400 mg (80%) of the crude product **7c**, which was purified by column chromatography on silica gel using 4% triethylamine in ethyl acetate in 73% yield. The spectral data of 3,4-dihydroisoquinoline **7c** were in accordance with the data in the literature.¹¹

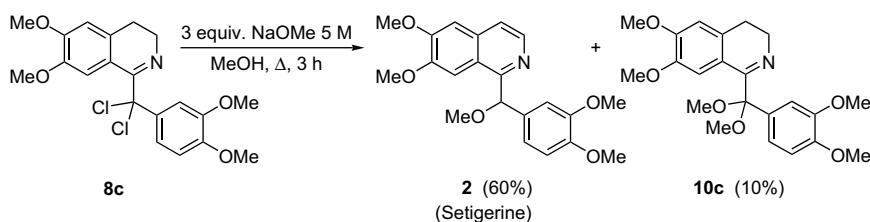
3.2.2.1. 1-(3-Methoxyphenyl)methyl-3,4-dihydro-6,7-dimethoxyisoquinoline (7b). White powder, mp 75–78 °C. ^1H NMR (CDCl_3): δ 2.65 (2H, t, $J=7.6$ Hz, H-4), 3.71–3.77 (2H, m, $\text{CH}_2\text{-N=}$), 3.73 (3H, s, OMe), 3.77 (3H, s, OMe), 3.87 (3H, s, OMe), 4.02 (2H, s, CH_2), 6.65 (1H, s, H-5), 6.73 (1H, dd, $J=8.3$, 2.3 Hz, H-4'), 6.86 (1H, s, H-2'), 6.90 (1H, dd, $J=7.6$, 2.3 Hz, H-6'), 6.97 (1H, s, H-8), 7.19 (1H, dd, $J=8.3$, 7.6 Hz, H-5'). ^{13}C NMR (CDCl_3): δ 25.8 (C-4), 43.6 ($\text{CH}_2\text{-Ar}$), 47.2 ($\text{CH}_2\text{-N=}$), 55.1 (OMe), 55.9 (OMe), 56.0 (OMe), 109.6 (C-5), 110.2 (C-8), 111.8 (C-2'), 114.2 (C-4'), 121.1 (C-6'), 121.6 (C-8a), 129.5 (C-5'), 131.8 (C-4a), 139.8 (C-1'), 147.2 (C-7), 150.7 (C-6), 159.8 (C-3'), 165.3 (C-1). IR (NaCl): ν_{max} 1640, 1600, 1561, 1514, 1460, 1340, 1300, 1280, 1150, 1040 cm^{-1} . MS m/z (%): 311 (M^+ , 70), 310 (100), 296 (21), 280 (37), 265 (9), 156 (7), 140 (10). Anal. Calcd for $\text{C}_{19}\text{H}_{21}\text{NO}_5$: C 73.29%, H 6.80%, N 4.50%; found: C 73.18%, H 6.88%, N 4.36%.

3.3. Synthesis of 1-(aryldichloromethyl)-3,4-dihydro-6,7-dimethoxyisoquinolines **8a–c**

3.3.1. General procedure

A vigorously stirred solution of 1.78 mmol of compound **7** in 40 ml of a 1:1 mixture of CH_2Cl_2 and CCl_4 was treated with 473 mg (3.56 mmol) of *N*-chlorosuccinimide, after which the reaction mixture was stirred at room temperature for 1–4 h. The reaction mixture was poured in water and extracted three times with CH_2Cl_2 . The combined extracts were washed with NaHCO_3 (5%) and brine, dried (MgSO_4), and evaporated in vacuo to give crude products **8a–c** (purity >95%). Compounds **8a–c** decomposed upon contact with silica gel during column chromatography and were used as such in the next step.

3.3.1.1. 1-(α,α -Dichlorobenzyl)-3,4-dihydro-6,7-dimethoxyisoquinoline (8a). Crude yield: 93%, colorless oil. ^1H NMR (CDCl_3): δ 2.64–2.80 (2H, m, CH_2), 3.39 (3H, s, OMe), 3.83 (3H, s, OMe), 3.96 (2H, t,



Scheme 4.

$J=7.6$ Hz, $\text{CH}_2\text{-N}$), 6.57 (1H, s, H-5), 6.67 (1H, s, H-8), 7.19–7.37 (3H, m, H-3', H-4', and H-5'), 7.68 (2H, d, $J=7.6$ Hz, H-2' and H-6'). ^{13}C NMR (CDCl_3): δ 25.8 (C-4), 48.0 (C-3), 55.4 (OMe), 55.7 (OMe), 91.2 (ArCCl_2), 110.0 (C-5), 111.5 (C-8), 117.7 (C-8a), 125.8 (C-2' and C-6'), 128.7 (C-3' and C-5'), 129.2 (C-4'), 132.9 (C-4a), 142.2 (C-1'), 146.2 (C-7), 150.6 (C-6), 162.1 (C-1). IR (NaCl): ν_{max} 1604, 1570, 1520, 1280 cm^{-1} . MS m/z (%): 349/351/353 (M^+ , 8), 314/316 (100), 264 (18), 186 (17), 139 (36).

3.3.1.2. 1-[(α,α -Dichloro-(3-methoxyphenyl)methyl]-3,4-dihydro-6,7-dimethoxyisoquinoline (8b). Crude yield 97%, colorless oil. ^1H NMR (CDCl_3): δ 2.74 (2H, t, $J=7.8$ Hz, CH_2), 3.40 (3H, s, OMe), 3.77 (3H, s, OMe), 3.87 (3H, s, OMe), 3.98 (2H, t, $J=7.8$ Hz, $\text{CH}_2\text{-N}$), 6.62 (1H, s, H-5), 6.68 (1H, s, H-8), 6.68–6.90 (1H, m, H-4'), 7.23–7.30 (2H, m, H-6' and H-5'), 7.27 (1H, m, H-2'). ^{13}C NMR (CDCl_3): δ 25.8 (C-4), 48.0 (C-3), 55.3 (OMe), 55.5 (OMe), 58.8 (OMe), 90.8 (ArCCl_2), 109.9 (C-5), 111.4 (C-8), 111.9 (C-2'), 114.6 (C-4'), 117.8 (C-8a), 118.1 (C-6'), 129.8 (C-5'), 133.0 (C-4a), 143.6 (C-1'), 146.3 (C-7), 150.7 (C-6), 159.8 (C-3'), 162.1 (C-1). IR (NaCl): ν_{max} 1600, 1515, 1257, 1150 cm^{-1} . MS m/z (%): no M^+ , 344/346 (M^+-Cl , 100), 309 (79), 294 (29), 266 (12), 265 (11), 172 (16), 133 (18).

3.3.1.3. 1-[(α,α -Dichloro-(3,4-dimethoxyphenyl)methyl]-3,4-dihydro-6,7-dimethoxyisoquinoline (8c). Crude yield 77%, colorless oil. ^1H NMR (CDCl_3): δ 2.69–2.74 (2H, m, CH_2), 3.45 (3H, s, OMe), 3.81 (3H, s, OMe), 3.86 (3H, s, OMe), 3.96 (3H, s, OMe), 3.87–3.96 (2H, m, $\text{CH}_2\text{-N}$), 6.64–6.75 (4H, m, $4\times=\text{CH}$), 7.88 (1H, s, $=\text{CH}$). ^{13}C NMR (CDCl_3): δ 25.2 (C-4), 47.4 (C-3), 55.5 (OMe), 55.7 (OMe), 56.1 (OMe), 56.3 (OMe), 89.7 (ArCCl_2), 110.0 ($=\text{CH}$), 110.2 ($=\text{CH}$), 111.2 ($=\text{CH}$), 114.1 ($=\text{CH}$), 117.1 ($=\text{CH}$), 130.6 ($=\text{C}_{\text{quat}}$), 133.6 ($=\text{C}_{\text{quat}}$), 137.7 ($=\text{C}_{\text{quat}}$), 146.1 ($=\text{C}_{\text{quat}}$), 147.1 ($=\text{C}_{\text{quat}}$), 149.9 ($=\text{C}_{\text{quat}}$), 151.1 ($=\text{C}_{\text{quat}}$), 163.2 (C-1). IR (NaCl): ν_{max} 1639, 1601, 1510, 1275, 1215 cm^{-1} . MS m/z (%): 409/411/413 (M^+ , 9), 407 (13), 373 (9), 372 (16), 134 (14), 133 (12), 120 (9), 119 (31), 105 (24), 99 (96), 56 (100).

3.4. Reaction of 1-(aryldichloromethyl)-3,4-dihydro-6,7-dimethoxyisoquinolines **8** with sodium methoxide: general procedure

3.4.1. Method A

A solution of 1 mmol of crude compounds **8** was reacted with 2.5 ml (5 mmol) of 2 M NaOMe in methanol at reflux for 3 h. The reaction mixture was poured in water and extracted with CH_2Cl_2 . The combined extracts were washed with 2 M hydrochloric acid, brine, and water, respectively, and dried (MgSO_4). After filtration, the solvent was removed in vacuo and the reaction crudes were purified by flash chromatography on silica gel (EtOAc/MeOH 9:1) to give pure products **9** and **10**.

3.4.2. Method B

A solution of 1 mmol of the crude α,α -dichloro-3,4-dihydro-6,7-dimethoxyisoquinoline **8c** in 0.6 ml (3 mmol) of 5 M NaOMe in methanol was boiled under reflux for 3 h. The reaction mixture was extracted three times with CH_2Cl_2 and the combined extracts were subsequently washed with 2 M hydrochloric acid, brine, and water. After drying over MgSO_4 and filtration, the solvent was removed in vacuum. The reaction crude was purified by flash chromatography on silica gel (EtOAc/MeOH 4:1) to give compound **2** (60% yield) and compound **10c** (10% yield).

3.4.3. Method C

To a solution of 1 mmol of the crude products **8a,b** in 3 ml of methanol was added dropwise 0.21 g (3 mmol) of triethylamine and the reaction mixture was refluxed for 3 h. This mixture was poured in cold water, after which it was extracted three times with

CH_2Cl_2 . The combined extracts were washed with 2 M hydrochloric acid, brine, water, and dried (MgSO_4). The solvent was removed in vacuo and the reaction crudes were purified by flash chromatography on silica gel (EtOAc/MeOH 4:1) to give pure compounds **10a,b**.

3.4.3.1. 1-(α -Methoxybenzyl)-6,7-dimethoxyisoquinoline (9a). Compound **9a** was synthesized in 60% yield according to method A (Section 3.4.1); white powder, mp 94–96 °C. ^1H NMR (CDCl_3): δ 3.49 (3H, s, OMe), 3.84 (3H, s, OMe), 3.94 (3H, s, OMe), 5.92 (1H, s, CHOMe), 7.01 (1H, s, H-5), 7.16–7.21 (1H, m, H-4'), 7.25–7.30 (2H, m, H-3' and H-5'), 7.45–7.49 (3H, m, H-2', H-4, and H-6'), 7.70 (1H, s, H-8), 8.41 (1H, m, H-3). ^{13}C NMR (CDCl_3): δ 55.8 (OMe), 55.9 (OMe), 57.4 (OMe), 87.7 (CHOMe), 104.8 (C-5), 105.0 (C-8), 119.8 (C-4), 122.0 (C-8a), 126.0 (C-2' and C-6'), 127.2 (C-4'), 128.1 (C-3' and C-5'), 134.1 (C-4a), 140.5 (C-3), 140.9 (C-1'), 149.4 (C-7), 152.4 (C-6), 157.1 (C-1). IR (KBr): ν_{max} 2940, 1560, 1505, 1480, 1255, 1160 cm^{-1} . MS m/z (%): 309 (M^+ , 59), 294 (82), 297 (100), 262 (18), 188 (15). Anal. Calcd for $\text{C}_{19}\text{H}_{19}\text{NO}_3$: C 73.77%, H 6.19%, N 4.53%; found: C 73.65%, H 6.08%, N 4.66%.

3.4.3.2. 1-[Methoxy-(3-methoxyphenyl)methyl]-6,7-dimethoxyisoquinoline (9b). Compound **9b** was synthesized in 81% yield according to method A (Section 3.4.1); colorless oil. ^1H NMR (CDCl_3): δ 3.48 (3H, s, OMe), 3.72 (3H, s, OMe), 3.86 (3H, s, OMe), 3.95 (3H, s, OMe), 5.89 (1H, s, CHOMe), 6.72–6.76 (1H, m, H-4'), 7.01 (1H, s, H-5), 7.04–7.07 (1H, m, H-6'), 7.07–7.11 (1H, m, H-2'), 7.16–7.22 (1H, m, H-5'), 7.46 (1H, m, H-4), 7.73 (1H, s, H-8), 8.41 (1H, m, H-3). ^{13}C NMR (CDCl_3): δ 55.1 (OMe), 55.9 (2 \times OMe), 57.4 (OMe), 87.5 (CHOMe), 104.5 (C-5), 105.0 (C-8), 111.8 (C-2'), 112.6 (C-4'), 118.4 (C-6'), 119.8 (C-4), 122.0 (C-8a), 129.1 (C-5'), 134.1 (C-4a), 140.5 (C-3), 142.6 (C-1'), 149.4 (C-7), 152.4 (C-6), 157.0 (C-3'), 159.6 (C-1). IR (NaCl): ν_{max} 2930, 1590, 1505, 1480, 1255, 1160 cm^{-1} . MS m/z (%): 339 (M^+ , 84), 324 (100), 309 (88), 294 (26), 262 (18), 188 (18), 119 (28). Anal. Calcd for $\text{C}_{20}\text{H}_{21}\text{NO}_4$: C 70.78%, H 6.24%, N 4.13%; found: C 70.65%, H 6.16%, N 4.28%.

3.4.3.3. 1-[Methoxy-(3,4-dimethoxyphenyl)methyl]-6,7-dimethoxyisoquinoline (Setigerin) (2). Compound **2** was obtained in 15% and 60% yield according to method A and method B (Sections 3.4.1 and 3.4.2), respectively. Mp 148–150 °C (from MeOH) (Ref. 4: 151 °C and Ref. 9: 145 °C). ^1H NMR data were in accordance with the data reported in the literature.⁹ Other experimental properties are as follows.

^{13}C NMR (CDCl_3): δ 55.7 (4 \times OMe), 55.8 (OMe), 86.9 (CHOMe), 104.3 (C-5), 104.9 (C-8), 109.5 (C-2'), 110.5 (C-6'), 118.5 (C-5'), 119.54 (C-4), 121.9 (C-4a), 133.4 (C-8a), 133.9 (C-1'), 140.4 (C-3'), 148.1 ($=\text{C}_{\text{quat}}$), 148.7 ($=\text{C}_{\text{quat}}$), 149.3 ($=\text{C}_{\text{quat}}$), 152.3 ($=\text{C}_{\text{quat}}$), 156.9 (C-1). IR (KBr): ν_{max} 1613, 1585, 1560, 1502, 1473, 1458, 1428, 1413, 1368, 1156, 1096, 1026 cm^{-1} . MS m/z (%): 369 (M^+ , 10), 354 (16), 339 (8), 235 (11), 220 (10), 189 (14), 119 (16), 103 (21), 73 (26), 59 (100). Anal. Calcd for $\text{C}_{21}\text{H}_{23}\text{NO}_5$: C 68.28%, H 6.28%, N 3.79%; found: C 68.14%, H 6.31%, N 3.75%.

3.4.3.4. 1-[(α,α -Dimethoxybenzyl)]-3,4-dihydro-6,7-dimethoxyisoquinoline (10a). Compound **10a** was synthesized in 11% and 96% yield according to method A and method C (Sections 3.4.1 and 3.4.3), respectively; colorless oil. ^1H NMR (CDCl_3): δ 2.63 (2H, t, $J=7.5$ Hz, CH_2), 3.17 (6H, s, C(OMe)_2), 3.63 (3H, s, OMe), 3.83 (3H, s, OMe), 3.85–3.91 (2H, m, CH_2N), 6.59 (1H, s, H-5), 7.26 (1H, s, H-8), 7.25–7.34 (3H, m, $3\times=\text{CH}$), 7.66–7.69 (2H, m, $2\times=\text{CH}$). ^{13}C NMR (CDCl_3): δ 25.9 (C-4), 47.6 (C-3), 49.4 (2 \times OMe), 55.8 (2 \times OMe), 101.9 (C(OMe)_2), 109.7 (C-5), 111.6 (C-8), 119.5 (C-8a), 126.9 (2 $\times=\text{CH}$), 128.1 (2 $\times=\text{CH}$), 128.3 ($=\text{CH}$), 132.2 (C-4a), 139.6 (C-1'), 146.6 (C-7), 150.2 (C-6), 163.8 (C-1). IR (NaCl): ν_{max} 1607, 1570, 1516, 1467, 1275, 1213, 1018 cm^{-1} . MS m/z (%): 341 (M^+ , 7), 326 (23), 311 (12),

396 (11), 151 (100), 105 (21). Anal. Calcd for $C_{20}H_{23}NO_4$: C 70.36%, H 6.79%, N 4.10%; found: C 70.52%, H 6.92%, N 4.29%.

3.4.3.5. 1-[Dimethoxy-(3-methoxyphenyl)methyl]-3,4-dihydro-6,7-dimethoxyisoquinoline (10b). Compound **10b** was synthesized in 16% and 82% yield according to method A and method C (Sections 3.4.1 and 3.4.3), respectively; colorless oil. 1H NMR ($CDCl_3$): δ 2.62 (2H, t, $J=7.5$ Hz, CH_2), 3.17 (6H, s, $C(OMe)_2$), 3.66 (3H, s, OMe), 3.76 (3H, s, OMe), 3.84 (3H, s, OMe), 3.85–3.90 (2H, m, CH_2N), 6.59 (1H, s, H-5), 6.78–6.82 (1H, m, H-4'), 7.19–7.26 (3H, m, $3\times=CH$), 7.30 (1H, s, H-8). ^{13}C NMR ($CDCl_3$): δ 25.9 (C-4), 47.5 (C-3), 49.4 ($2\times OMe$), 55.2 (OMe), 55.8 ($2\times OMe$), 101.7 ($C(OMe)_2$), 109.7 (C-5), 110.6 (C-8), 112.5 (C-2'), 113.8 (C-4'), 119.4 (C-6'), 119.6 (C-8a), 129.1 (C-5'), 132.2 (C-4a), 141.3 (C-1'), 146.6 (C-7), 150.2 (C-6), 159.5 (C-3'), 163.8 (C-1). IR (NaCl): ν_{max} 1605, 1570, 1516, 1470, 1402, 1275, 1018 cm^{-1} . MS m/z (%): 371 (M^+ , 14), 356 (29), 341 (11), 326 (14), 207 (15), 196 (25), 181 (100), 165 (23), 135 (19). Anal. Calcd for $C_{21}H_{25}NO_5$: C 67.91%, H 6.78%, N 3.77%; found: C 67.78%, H 6.68%, N 3.89%.

3.4.3.6. 1-[Dimethoxy-(3,4-dimethoxyphenyl)methyl]-3,4-dihydro-6,7-dimethoxyisoquinoline (10c). Compound **10c** was synthesized in 74% and 10% yield according to method A and method B (Sections 3.4.1 and 3.4.2), respectively; colorless oil. 1H NMR ($CDCl_3$): δ 2.59 (2H, t, $J=7.6$ Hz, CH_2), 3.14 (6H, s, $C(OMe)_2$), 3.65 (3H, s, OMe), 3.81–3.92 (2H, m, CH_2N), 3.81 (3H, s, OMe), 3.82 (6H, s, $2\times OMe$), 6.57 (1H, s, H-5), 6.78 (1H, d, $J=8.6$ Hz, H-6'), 7.11 (1H, m, H-2'), 7.23 (1H, d, $J=8.6$ Hz, H-5'), 7.27 (1H, s, H-8). ^{13}C NMR ($CDCl_3$): δ 25.8 (C-4), 47.5 (C-3), 49.2 ($2\times OMe$), 55.6 ($2\times OMe$), 55.7 ($2\times OMe$), 101.6 ($C(OMe)_2$), 109.5 (C-5), 109.7 (C-8), 110.2 (C-5'), 110.5 (C-1'), 119.4 (C-6'), 131.9 (C-4a), 132.0 (C-5a), 146.5 ($=C_{quat}$), 148.5 ($=C_{quat}$), 148.7 ($=C_{quat}$), 150.0 ($=C_{quat}$), 167.7 (C-1). IR (NaCl): ν_{max} 1599,

1564, 1507, 1457, 1402, 1265, 1207, 1109, 1025 cm^{-1} . MS m/z (%): 401 (M^+ , 9), 386 (22), 369 (26), 355 (22), 354 (56), 324 (25), 336 (11), 212 (12), 211 (100), 196 (20), 165 (34), 151 (23). Anal. Calcd for $C_{22}H_{27}NO_6$: C 65.82%, H 6.78%, N 3.49%; found: C 65.68%, H 6.65%, N 3.63%.

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