DOI 10.1007/s10600-015-1203-1
Chemistry of Natural Compounds, Vol. 51, No. 1, January, 2015

AMINOMETHYLATION OF 1-ARYL-6,7-DIMETHOXY-1,2,3,4-TETRAHYDROISOQUINOLINES BY DIHYDROQUERCETIN

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Mannich reaction of dihydroquercetin with a series of 1-aryl-6,7-dimethoxytetrahydroisoquinolines synthesized heterocyclic mono- and di-substituted conjugates of dihydroquercetin and N*-hydroxymethyl isoquinoline derivatives.*

Keywords: dihydroquercetin, 1-aryl-6,7-dimethoxytetrahydroisoquinoline, Mannich reaction, *N*-hydroxymethyl isoquinoline derivatives.

Flavonoids belong to a large class of natural heterocyclic compounds, possess a broad spectrum of biological activity [1], and can be chemically modified to produce new pharmacologically active compounds. Dihydroquercetin (DHQ, **1**) is currently one of the most common and available flavonoids [2, 3]. It is a unique natural free-radical acceptor and is recognized as a standard for very high antioxidant activity.

Mannich reactions with primary and secondary amines are known to produce high yields of DHQ aminomethyl derivatives [4–7]. It was shown that mono- and di-substituted products could be obtained depending on the reagent ratio and order of addition. It was established that the Mannich reaction could be carried out both with formation (isolation) of an intermediate complex of DHQ with secondary amines and in a three-component mixture [4, 5, 7]. Primarily DHQ 6-aminomethyl derivatives were obtained with an equimolar reagent ratio.

The goal of the present work was to synthesize mono-substituted DHQ derivatives. A series of 1-aryl-6,7-dimethoxytetrahydroisoquinolines (**2a**–**h**) that were prepared by us earlier were used as the amines [8, 9].

The reaction was carried out in *i*-PrOH at 20–25°C with DHQ–isoquinoline, 1:1 [4]. However, DHQ complexes with the isoquinolines (**2a**–**h**) were not observed. Addition of equimolar amounts of formaldehyde formed mono- and di-substituted DHQ products **3a**–**f** and **5b** and **g**, respectively. In addition, isoquinoline *N*-hydroxymethyl derivatives **4f**–**h** appeared as side products.

The direction of the reaction (Scheme 1, A, B, or C) and product yield depended on the structure of the starting isoquinoline. Use of isoquinolines with electron-donating substituents (methoxy and methylenedioxy groups) gave derivatives **3a** and **c**–**f** in good yields (pathway A) with DHQ reacting practically completely. The electron-accepting nitro group in isoquinoline **2b** led to the formation of both mono- (**3b**) and di-substituted (**5b**) products (pathways A and C). Bromo-substituted isoquinoline **2g** afforded only the di-substituted DHQ product **5g** (pathway C).

1-(2′-Hydroxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**2h**) under the above conditions did not undergo a Mannich reaction. The only reaction product was hydroxymethyl derivative **4h**. Starting DHQ was completely recovered. The hydroxymethyl derivatives were also obtained in small amounts (7–10%) for bromo-substituted isoquinolines **2f** and **2g**. Resonances of N–CH_2–OH protons in PMR spectra of these compounds confirmed that 2-hydroxymethyl isoquinoline derivatives **4f**–**h** had formed.

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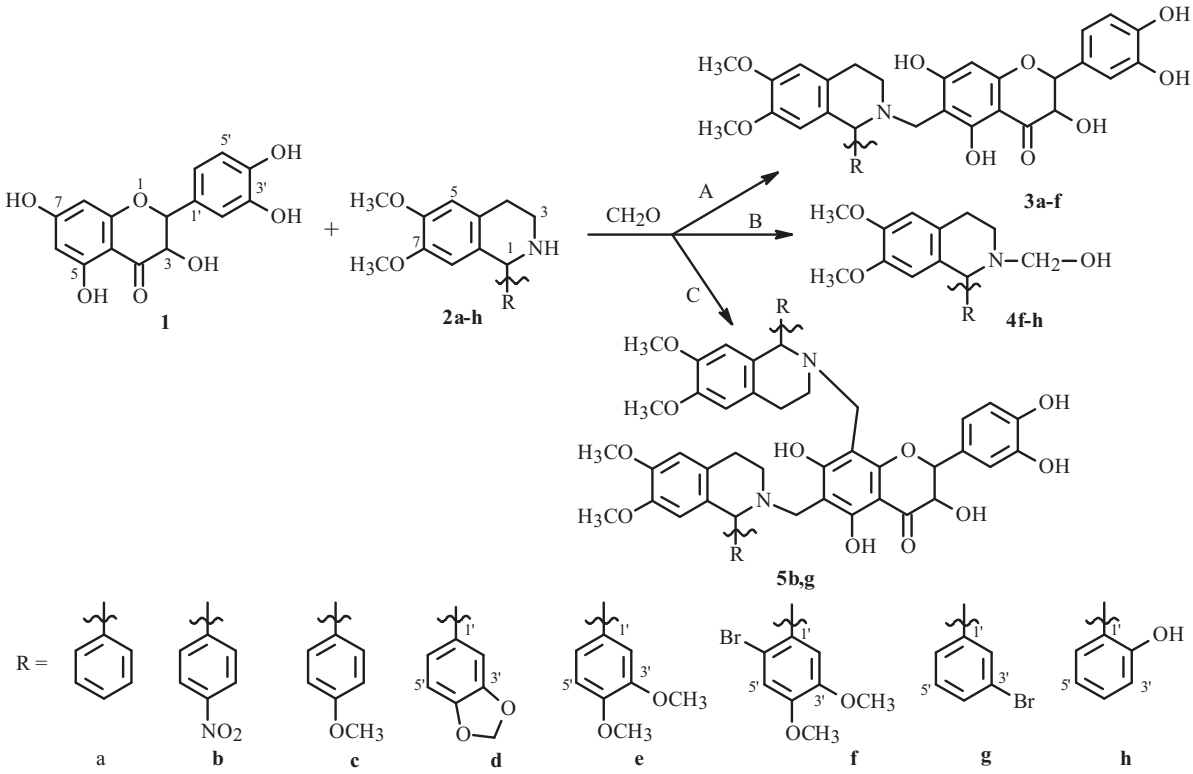

Scheme 1

The synthesized compounds were characterized using IR and NMR spectroscopy. IR spectra of the conjugates showed strong absorption bands for hydroxyls (3435–3204 cm^{-1}) and carbonyls (1639–1633 cm^{-1}) of the DHQ fragment. PMR spectra exhibited resonances for H-3 at 4.35–4.50 ppm; doublets of doublets for H-2, 4.66–4.98; and singlets for H-8, 5.79–5.87. These were characteristic of the DHQ fragment. In addition, singlets for H-1 at 4.81–4.94 and aromatic H-5 at 6.76–6.87 and H-8 at 6.21–6.28 were characteristic of the isoquinoline part.

Resonances of H-3 and H-4 of the isoquinoline N–CH_2–CH_2 fragment in PMR spectra of **3a**–**f** and **5b** and **g** were assigned by analyzing COSY NMR spectra using **3d** as an example. The ^{1}H COSY spectrum of **3d** contained a mutually coupled 4-spin system at 2.48–3.08 ppm that could only be methylene protons H-3 and H-4 in this structure. Three very weak cross-peaks at 2.5–3.1 ppm enabled the H-3 and H-4 resonances to be assigned. The two inner resonances of this group (δ 2.68 and 2.83 ppm) formed weak cross-peaks with the resonance for aromatic H-5 (6.46 ppm) and; therefore, were assigned to H-4. The resonance at 2.52 ppm showed a weak cross-peak at 3.57 ppm that was characteristic for one of the N–CH_2–Ar methylene protons and; therefore, could be assigned to H-3.

Thus, amination of DHQ derivatives by 1-aryl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines produced mono- and di-substituted DHQ conjugates and hydroxymethyl derivatives of the starting isoquinolines.

EXPERIMENTAL

IR spectra were recorded from KBr pellets on a System 2000 FTIR instrument (PerkinElmer). PMR and ^{13}C NMR spectra were recorded from DMSO-d_6 solutions with HMDS internal standard on Unity-400 and Bruker AV-400 and DRX-500 spectrometers. TLC R_f values were determined on LS 5/40 silica gel plates using $CHCl_3$–MeOH (4:1, 1; 6:1, 2; 8:1, 3). Melting points of all synthesized compounds were determined on a Boetius apparatus. 1-Aryl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines (**2a**–**h**) were prepared by the literature method [8, 9].

Reaction of 1-Aryl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines (2a–h) with DHQ (1). General Method. A solution of 1-aryl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (0.667 mmol) in *i*-PrOH (5 mL) was stirred, treated dropwise over 10 min with a solution of DHQ (0.2 g, 0.667 mmol) in *i*-PrOH (5 mL), held at 20–25°C for 0.5 h, and treated dropwise with formalin solution (30%, 0.06 mL, 0.667 mmol, d = 1.092). A precipitate began to form immediately. The mixture was left

for 12 h. The course of the reaction was monitored by TLC. The precipitate was filtered off and rinsed with *i*-PrOH, hexane–Et_2O (1:1), $CHCl_3$–Et_2O (1:1), and $CHCl_3$. The precipitates polymerized in benzene and dioxane.

Equimolar amounts of DHQ (0.2 g, 0.667 mmol) and formalin solution (30%, 0.06 mL, 0.667 mmol) were used in the reactions described below.

2-(3,4-Dihydroxyphenyl)-6-{[6,7-dimethoxy-1-phenyl-3,4-dihydroisoquinolin-2(1*H*)-yl]methyl}-3,5,7-trihydroxychroman-4-one (3a). 1-Phenyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**2a**) produced **3a**. Yield 0.32 g (81%), mp 162–166°C (*i*-PrOH), R_f 0.59 (system 1). IR spectrum (KBr, ν_{max}, cm^{-1}): 3433 (OH), 1638 (C=O), 1516, 1449 (C=C), 1267 (C–O). ^{1}H NMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): a) DHQ fragment: 3.62 (1H, dd, J = 4.7, 14.2, N-CH_2), 3.78 (1H, d, J = 14.2, NCH_2), 4.45 (1H, dd, J = 5.6, 11.0, H-3), 4.92 (1H, t, J = 11.0, H-2), 5.67 (1H, br.s, 3-OH), 5.79 (1H, br.s, H-8), 6.70 (2H, s, H-5′,6′), 6.75 (1H, s, H-2′), 8.90, 8.94 (each 1H, br.s, 3′,4′-OH), 12.29 (1H, br.s, 5-OH), b) 1-phenyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline fragment: 2.64 (1H, m, H_a-3), 2.81 (2H, m, H-4), 2.96 (1H, m, H_e-3), 3.46 (3H, s, 7-OCH_3), 3.71 (3H, s, 6-OCH_3), 4.82 (1H, s, H-1), 6.21 (1H, br.s, H-8), 6.83 (1H, s, H-5), 7.15–7.38 (5H, m, Ar-H). ^{13}C NMR spectrum (δ, ppm): a) DHQ fragment: 48.23 (CH_2–N), 71.84 (C-3), 83.33 (C-2), 95.48 (C-8), 100.29 (C-6), 101.37 (C-4a), 115.42 (C-2′), 115.67 (C-5′), 119.72 (C-6′), 128.00 (C-1′), 145.25 (C-3′), 146.09 (C-4′), 161.01 (C-8a), 161.63 (C-5), 168.36 (C-7), 198.14 (C-4); b) 1-phenyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline fragment: 21.44 (C-4), 44.63 (C-3), 55.74 (6-OCH_3), 55.84 (7-OCH_3), 66.15 (C-1), 111.73 (C-8), 112.04 (C-5), 126.16 (C-8a), 127.83–128.90 (5C, Ph), 129.93 (C-4a), 147.44 (C-6), 148.06 (C-7).

Reaction of 1-(4′-Nitrophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline with DHQ. 1-(4′-Nitrophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**2b**, 0.21 g, 0.667 mmol) produced a mixture of **3b** and **5b**, R_f 0.63 and 0.57 (system 1). The yield of the mixture was 0.27 g (66%). Products **3b** and **5b** were purified by preparative chromatography over SiO_2 using system 1.

2-(3,4-Dihydroxyphenyl)-6-{[6,7-dimethoxy-1-(4-nitrophenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]methyl}-3,5,7-trihydroxychroman-4-one (3b), mp 178–182°C (*i*-PrOH), R_f 0.63 (system 1), yield 36%. IR spectrum (KBr, ν_{max}, cm^{-1}): 3075 (OH), 2939 (CH_2), 1639 (C=O), 1519 (NO_2), 1463 (C=C), 1349 (C–NO_2), 1265, 1122 (C–O). ^{1}H NMR spectrum (500 MHz, DMSO-d_6, δ, ppm, J/Hz): a) DHQ fragment: 3.68 (2H, resonance overlapped, N–CH_2), 4.49 (1H, br.s, J = 11.0, H-3), 4.94 (1H, m, H-2), 5.78 (1H, br.s, 3-OH), 5.87 (1H, s, H-8), 6.74 (2H, s, H-5′, 6′), 6.78 (1H, s, H-2′), 9.00, 9.06 (each 1H, br.s, 3′, 4′-OH), 12.33 (1H, br.s, 5-OH); b) 1-(4′-nitrophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline fragment: 2.66 (1H, m, H_a-3), 2.83 (2H, m, H-4), 2.97 (1H, m, H_e-3), 3.51 and 3.74 (each 3H, s, 6, 7-OCH_3), 4.94 (1H, s, H-1), 6.26 (1H, s, H-8), 6.86 (1H, s, H-5), 7.53 (2H, d, J = 8.5, H-2′, 6′), 8.20 (2H, d, J = 8.5, H-3′, 5′).

2-(3,4-Dihydroxyphenyl)-6,8-*bis*{[6,7-dimethoxy-1-(4-nitrophenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]methyl}-3,5,7-trihydroxychroman-4-one (5b), mp 170–173°C (*i*-PrOH), R_f 0.57 (system 1), yield 24%. IR spectrum (KBr, ν_{max}, cm^{-1}): 3435 (OH), 2924 (CH_2), 1633 (C=O), 1519 (NO_2), 1451 (C=C), 1348 (C–NO_2), 1261, 1122 (C–O). ^{1}H NMR spectrum (500 MHz, DMSO-d_6, δ, ppm, J/Hz): a) DHQ fragment: 3.46 (4H, resonances overlapped, 2N–CH_2), 4.46 (1H, d, J = 11.6, H-3), 4.81 (1H, d, J = 11.6, H-2), 5.75 (1H, br.s, 3-OH), 6.69 (3H, s, H-2′, 5′, 6′), 8.93, 9.06 (each 1H, br.s, 3′, 4′-OH), 12.37 (1H, br.s, 5-OH); b) two 1-(4′-nitrophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline fragments: 2.62 (2H, m, H_a-3, 3), 2.79 (4H, m, H-4, 4), 2.90 (2H, m, H_e-3, 3), 3.45, 3.47 (each 3H, s, 7, 7-OCH_3), 3.69, 3.71 (each 3H, s, 6, 6-OCH_3), 4.92, 4.93 (each 1H, br.s, H-1, 1), 6.18, 6.24 (each 1H, s, H-8, 8), 6.75, 6.83 (each 1H, s, H-5, 5), 7.29, 7.46 (each 2H, m, H-2′, 2′, 6′, 6′), 7.96 (4H, m, H-3′, 3′, 5′, 5′).

2-(3,4-Dihydroxyphenyl)-6-{[6,7-dimethoxy-1-(4-methoxyphenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]methyl}-3,5,7-trihydroxychroman-4-one (3c). 1-(4′-Methoxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**2c**, 0.2 g, 0.667 mmol) afforded **3c**. Yield 0.31 g (78%), mp 180–185°C (*i*-PrOH), R_f 0.57 (system 2). IR spectrum (KBr, ν_{max}, cm^{-1}): 3423 (OH), 1642 (C=O), 1514, 1463 (C=C), 1255 (C–O). ^{1}H NMR spectrum (500 MHz, DMSO-d_6, δ, ppm, J/Hz): a) DHQ fragment: 3.67 (1H, dd, J = 4.8, 14.3, N–CH_2), 3.82 (1H, d, J = 14.3, N–CH_2), 4.48 (1H, dd, J = 5.5, 11.0, H-3), 4.96 (1H, t, J = 10.6, H-2), 5.81 (1H, s, H-8), 6.74 (2H, s, H-5′, 6′), 6.78 (1H, s, H-2′), 8.97 (2H, br.s, 3′, 4′-OH), 12.31 (1H, br.s, 5-OH); b) 1-(4′-methoxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline fragment: 2.68 (1H, m, H_a-3), 2.85 (2H, m, H-4), 2.99 (1H, m, H_e-3), 3.51 (3H, s, 7-OCH_3), 3.74 (6H, s, 6, 4′-OCH_3), 4.82 (1H, s, H-1), 6.25 (1H, s, H-8), 6.87 (1H, s, H-5), 6.91 (2H, d, J = 8.5, H-3′, 5′), 7.10 (2H, d, J = 8.5, H-2′, 6′). ^{13}C NMR spectrum (δ, ppm): a) DHQ fragment: 48.22 (CH_2–N), 71.73 (C-3), 83.20 (C-2), 95.46 (C-8), 100.08, 101.00 (C-4a, 6), 115.32 (C-2′), 115.55 (C-5′), 119.55 (C-6′), 128.22 (C-1′), 145.14 (C-3′), 145.96 (C-4′), 160.79 (C-8a), 161.71 (C-5), 168.62 (C-7), 197.88 (C-4); b) 1-(4′-methoxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline fragment: 21.24 (C-4), 44.48 (C-3), 55.25 (6-OCH_3), 55.66 (7-OCH_3), 55.74 (4′-OCH_3), 65.29 (C-1), 111.67 (C-8), 112.08 (C-5), 113.90 (C-2′), 113.90 (C-3′), 125.99 (C-1′), 128.05 (C-5′), 128.22 (C-6′), 130.97 (C-8a), 133.31 (C-4a), 147.40 (C-6), 148.01 (C-7), 158.87 (C-4′).

2-(3,4-Dihydroxyphenyl)-6-{[1-(3,4-methylenedioxyphenyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl]methyl}-3,5,7-trihydroxychroman-4-one (3d). 1-(3′,4′-Methylenedioxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**2d**, 0.21 g, 0.67 mmol) afforded **3d**. Yield 0.34 g (83%), mp 176–180°C (*i*-PrOH), R_f 0.34 (system 2). IR spectrum (KBr, ν_{max}, cm^{-1}): 3204 (OH), 1639 (C=O), 1516, 1488 (C=C), 1252 (C–O). ^{1}H NMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): a) DHQ fragment: 3.67 (1H, dd, J = 3.3, 14.3, N–CH_2), 3.79 (1H, d, J = 14.3, N–CH_2), 4.49 (1H, dd, J = 3.9, 11.1, H-3), 4.96 (1H, dd, J = 7.8, 11.1, H-2), 5.83 (1H, s, H-8), 6.74 (2H, s, H-5′, 6′), 6.87 (1H, s, H-2′), 9.00 (2H, br.s, 3′, 4′-OH), 12.33 (1H, br.s, 5-OH); b) 1-(3′4′-methylenedioxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline fragment: 2.65 (1H, m, H_a-3), 2.82 (2H, m, H-4), 2.99 (1H, m, H_e-3), 3.52 (3H, s, 7-OCH_3), 3.74 (3H, s, 6-OCH_3), 4.77 (1H, s, H-1), 6.01 (2H, d, J = 3.4, 3′, 4′-OCH_2O), 6.27 (1H, s, H-8), 6.68 (1H, s, H-2′), 6.69 (1H, d, J = 6.4, H-6′), 6.76 (1H, s, H-5), 6.88 (1H, d, J = 8.5, H-5′). ^{13}C NMR spectrum (δ, ppm): a) DHQ fragment: 47.87 (CH_2–N), 71.51 (C-3), 82.99 (C-2), 95.20 (C-8), 99.93, 101.09 (C-4a, 6), 115.09 (C-2′), 115.33 (C-5′), 119.37 (C-6′), 127.69 (C-1′), 144.92 (C-3′), 145.76 (C-4′), 160.67 (C-8a), 161.48 (C-5), 168.08 (C-7), 197.83 (C-4); b) 1-(3′4′-methylenedioxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline fragment: 25.49 (C-4), 44.53 (C-3), 55.40 (6-OCH_3), 55.48 (7-OCH_3), 65.60 (C-1), 101.09 (C-7′), 107.78 (C-5′), 109.36 (C-2′), 111.37 (C-8), 111.64 (C-5), 123.28 (C-6′), 125.80 (C-1′), 127.99 (C-8a), 135.32 (C-4a), 146.68 (C-6), 147.12 (C-7), 147.31 (C-3′), 147.74 (C-4′).

2-(3,4-Dihydroxyphenyl)-6-{[1-(3,4-dimethoxyphenyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl]methyl}-3,5,7-trihydroxychroman-4-one (3e). 1-(3′,4′-Dimethoxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**2e**, 0.22 g, 0.667 mmol) afforded **3e**. Yield 0.35 g (84%), mp 174–178°C (*i*-PrOH), R_f 0.71 (system 2). IR spectrum (KBr, ν_{max}, cm^{-1}): 3434 (OH), 1641 (C=O), 1516, 1462, 1449 (C=C), 1261 (C–O). ^{1}H NMR spectrum (500 MHz, DMSO-d_6, δ, ppm, J/Hz): a) DHQ fragment: 3.70 (2H, resonance overlapped, N–CH_2), 4.48 (1H, dd, J = 3.6, 11.0, H-3), 4.95 (1H, t, J = 10.9, H-2), 5.82 (1H, s, H-8), 6.74 (2H, s, H-5′, 6′), 6.87 (1H, s, H-2′), 8.98 (2H, br.s, 3′, 4′-OH), 12.36 (1H, br.s, 5-OH); b) 1-(3′,4′-dimethoxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline fragment: 2.68 (1H, m, H_a-3), 2.85 (2H, m, H-4), 3.03 (1H, m, H_e-3), 3.51 (3H, s, 7-OCH_3), 3.69 (3H, s, 6-OCH_3), 3.74 (3H, s, 3′-OCH_3), 3.75 (1H, s, 4′-OCH_3), 4.47 (1H, d, J = 1.9, H-1), 6.28 (1H, s, H-8), 6.67 (2H, dd, J = 1.8, 8.2, H-6′), 6.77 (1H, s, H-5), 6.80 (1H, d, J = 1.8, H-2′), 6.91 (1H, d, J = 8.2, H-5′). ^{13}C NMR spectrum (δ, ppm): a) DHQ fragment: 48.36 (CH_2–N), 71.78 (C-3), 83.24 (C-2), 95.44 (C-8), 100.11, 101.18 (C-4a, 6), 115.35 (C-2′), 115.58 (C-5′), 119.59 (C-6′), 128.24 (C-1′), 145.17 (C-3′), 146.00 (C-4′), 160.84 (C-8a), 161.72 (C-5), 168.60 (C-7), 197.95 (C-4); b) 1-(3′,4′-dimethoxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline fragment: 21.44 (C-4), 45.07 (C-3), 55.65 (6-OCH_3), 55.67 (7-OCH_3), 55.67 (3′-OCH_3), 55.79 (4′-OCH_3), 65.96 (C-1), 111.56 (C-8), 111.67 (C-5), 112.12 (C-6′), 113.27 (C-5′), 122.26 (C-2′), 125.99 (C-1′), 127.97 (C-8a), 133.88 (C-4a), 147.37 (C-6), 148.02 (C-7), 148.54 (C-3′), 148.78 (C-4′).

Reaction of 1-(6′-Bromo-3′,4′-dimethoxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline with DHQ. 1-(6′-Bromo-3′,4′-dimethoxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**2f**, 0.27 g, 0.667 mol), DHQ (**1**, 0.2 g, 0.667 mmol), and formalin solution (30%, 0.06 mL, 0.667 mmol) afforded a mixture of **3f** and **4f**. The yield of the mixture was 0.31 g (65%), R_f 0.67 and 0.71 (system 2). The products were purified by preparative chromatography over silica gel (system 2).

2-(3,4-Dihydroxyphenyl)-6-{[1-(6′-bromo-3′,4′-dimethoxyphenyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl]methyl}-3,5,7-trihydroxychroman-4-one (3f). Yield 50%, mp 168–172°C (*i*-PrOH), R_f 0.67 (system 2). ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): a) DHQ fragment: 3.70 (2H, s, NCH_2), 4.33 (1H, d, J = 11.4, H-3), 4.66 (1H, br. resonance, H-2), 5.81 (1H, s, H-8), 6.72, 6.78 (each 1H, d, J = 7.7, H-5′, 6′), 6.88 (1H, s, H-2′); b) 1-(6′-bromo-3′,4′-dimethoxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline fragment: 2.70, 3.03, 3.21 (4H, all m, H-3, 4), 3.59 (3H, s, 7-OCH_3), 3.64 (3H, s, 6-OCH_3), 3.81 (6H, s, 3′, 4′-OCH_3), 5.13 (1H, s, H-1), 6.10 (1H, s, H-8), 6.56 (1H, s, H-2′), 6.73 (1H, s, H-5), 6.99 (1H, s, H-5′).

1-(6′-Bromo-3′,4′-dimethoxyphenyl)-2-hydroxymethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (4f). Yield ~10%, R_f 0.71 (system 2). ^{1}H NMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.79 (2H, br.s, H-4), 2.89 (2H, br.s, H-3), 3.68 (6H, s, 6, 7-OCH_3), 3.71 (6H, s, 3′, 4′-OCH_3), 4.49 (1H, d, J = 11.0, N–CH_2), 4.96 (1H, d, J = 11.0, N–CH_2), 5.79 (1H, s, H-1), 6.68 (1H, s, H-8), 6.70 (1H, s, H-5), 6.74 (1H, s, H-2′), 6.87 (1H, s, H-5′).

Reaction of 1-(3′-Bromophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline with DHQ. 1-(3′-Bromophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**2g**, 0.23 g, 0.667 mmol) afforded a mixture of **4g** and **5g**. The overall yield of the mixture was 0.19 g (44%), R_f 0.42 and 0.79 (system 3).

1-(3′-Bromophenyl)-2-hydroxymethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (4g). Yield ~10%, mp 268–272°C (MeOH), R_f 0.42 (system 3). ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.86, 2.99, 3.07, 3.17 (each 1H, m,

H-3, 4), 3.58 (2H, s, N-CH_2), 3.61 (3H, s, 7-OCH_3), 3.82 (3H, s, 6-OCH_3), 4.83 (1H, br.s, OH), 5.24 (1H, s, H-1), 6.16 (1H, s, H-8), 6.58 (1H, s, H-5), 7.16 (2H, m, H-5′, 6′), 7.36 (1H, s, H-2′), 7.40 (1H, d, J = 6.7, H-4′).

2-(3,4-Dihydroxyphenyl)-6,8-*bis*{[6,7-dimethoxy-1-(3′-bromophenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]methyl}-3,5,7-trihydroxychroman-4-one (5g). Yield 24%, mp 166–170°C (*i*-PrOH), R_f 0.79 (system 3). ^{1}H NMR spectrum (500 MHz, DMSO-d_6, δ, ppm, J/Hz): a) DHQ fragment: 3.62, 3.70 (each 2H, m, 2N–CH_2), 4.50 (1H, d, J = 11.5, H-3), 4.96 (1H, dd, J = 4.4, 11.3, H-2), 5.76 (1H, br.s, 3-OH), 6.74 (2H, s, H-5′, 6′), 6.77 (1H, s, H-2′), 9.0 (2H, br.s, 3′, 4′-OH), 12.36 (1H, br.s, 5-OH); b) two 1-(3′-bromophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline fragments: 2.64 (2H, m, H_a-3, 3), 2.81 (4H, m, H-4, 4), 2.94 (2H, m, H_e-3, 3), 3.50, 3.52 (each 3H, s, 7, 7-OCH_3), 3.72, 3.74 (each 3H, s, 6, 6-OCH_3), 4.83 (1H, s, H-1), 5.87 (1H, s, H-1), 6.22 (1H, s, H-8), 6.29 (1H, s, H-8), 6.72 (1H, s, H-5), 6.87 (1H, s, H-5), 7.19–7.33(4H, m, Ar–H), 7.41–7.49 (4H, m, Ar–H).

1-(2′-Hydroxyphenyl)-2-hydroxymethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (4h). 1-(2′-Hydroxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**2h**, 0.19 g, 0.667 mmol) afforded **4h**. Yield 0.17 g (44%), mp 201–203°C (*i*-PrOH), R_f 0.54 (system 3). ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.62 (1H, m, H_e-4), 3.00 (2H, m, H-3), 3.13 (1H, m, H_a-4), 3.80 (3H, s, 7-OCH_3), 3.88 (3H, s, 6-OCH_3), 4.89 (1H, d, J = 11.0, N–CH_2), 5.26 (1H, d, J = 11.0, N–CH_2), 5.27 (1H, s, H-1), 6.59 (1H, s, H-8), 6.64 (2H, m, H-3′, 6′), 6.74 (1H, s, H-5), 7.03 (2H, m, H-4′, 5′).

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