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AMINOMETHYLATION OF AFROMOSIN, CLADRASTIN, AND THEIR 2-METHYL DERIVATIVES

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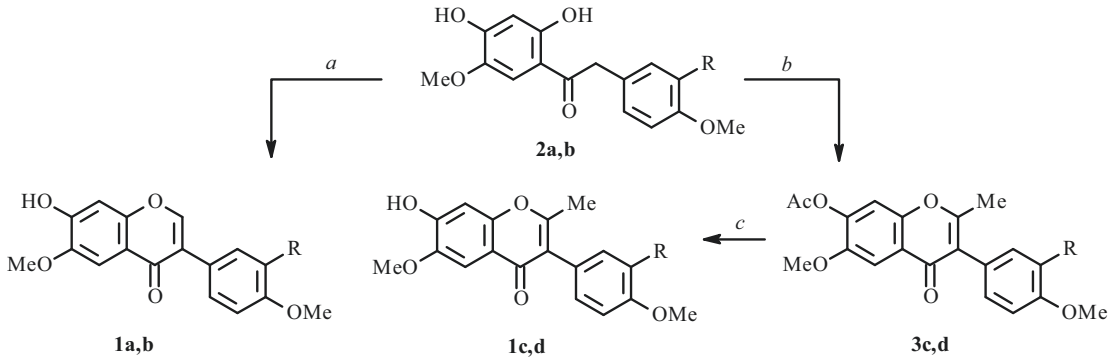
Aminomethylation of the natural isoflavones afromosin and cladrastin and their 2-methyl derivatives was studied. Several new Mannich bases of 7-hydroxy-6-methoxyisoflavones were synthesized under Mannich reaction conditions using aminals of secondary amines.

Keywords: isoflavone, afromosin, cladrastin, aminomethylation, Mannich base, aminal.

Mannich bases of isoflavonoids were shown by us earlier to be promising intermediates for designing biologically active compounds [1, 2].

In continuation of research on aminomethylation of flavonoids, we turned our attention to the natural 6-methoxy-substituted isoflavones afromosin (also called afrormosin) (**1a**), which occurs in plants of the family Leguminosae such as *Afromosia elata* Harms [3], *Wistaria floridunda* [4], *Amphimas pterocarpoides* [5], *Myroxylon balsamium* L. Harms [6], *Baptisia australis* [7], *Glycyrrhiza glabra* [8], and *Hedysarum theinum* [9] and cladrastin (**1b**), which was isolated from *Cladrastis lutea* [10], *C. platycarpa* [11], and *Millettia griffoniana* [12].



a,c: R = H; **b,d:** R = OMe

a. $POCl_3$, DMF, $Et_2O{\cdot}BF_3$; *b*. Ac_2O, Et_3N; *c*. HCl, EtOH

The positions of the substituents on flavonoid ring A have a great influence on the direction and regioselectivity of electrophilic attack under Mannich reaction conditions and on the ability to perform electrophilic substitution. Our research showed that 5,7-dihydroxyflavonoids act as CH substrates in the Mannich reaction and form the corresponding 6,8-bis(aminomethyl) derivatives [13–16]. The Mannich reaction of 7-hydroxy-5-methoxyisoflavones occurred regioselectively at the C-8 atom [17] whereas aminomethylation of 7-methoxy-5-hydroxyisoflavones formed a mixture of 6-aminomethyl and 8-aminomethyl derivatives with the C-6 isomer dominating [1]. Mannich reaction of 7-hydroxy-8-methylisoflavones gave the corresponding 6-aminomethyl derivatives [2].

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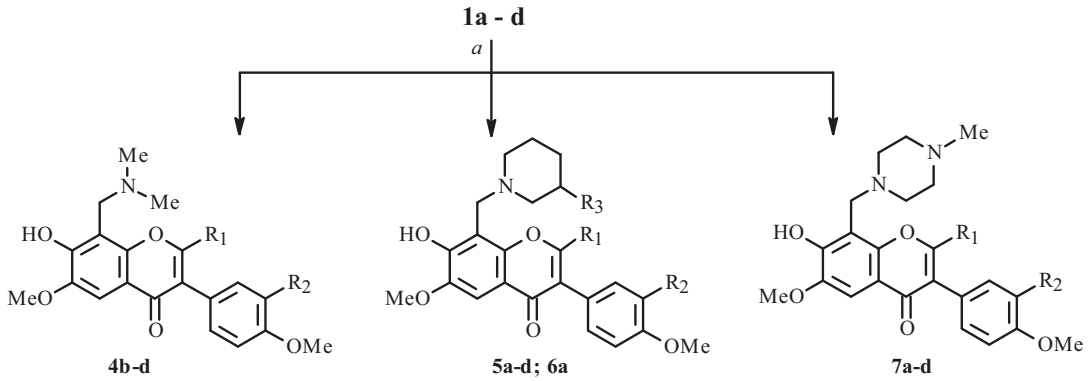
The natural isoflavones afromosin (**1a**) and cladrastin (**1b**) and their 2-methyl derivatives (**1c** and **1d**) were of interest for studying aminomethylation of a chromone core containing electron-donating hydroxyl and methoxyl groups situated in a discordant orientation.

The starting compounds for constructing the chromone core were the corresponding 2,4-dihydroxy-5-methoxydeoxybenzoins **2a** and **2b**, which were prepared using a Hoesch reaction. Afromosin (**1a**) has been synthesized via formylation followed by heterocyclization of 2-hydroxydeoxybenzoin under Gattermann reaction conditions using $Zn(CN)_2$ and HCl [3] or 1,3,5-triazine and $Et_2O{\cdot}BF_3$ [18]. Also, a one-pot method for synthesizing **1a** using the reaction of 2-hydroxydeoxybenzoin prepared under Friedel–Crafts reaction conditions with DMF and $MeSO_2Cl$ was reported [19]. Cladrastin (**1b**) was also synthesized via formylation under Gattermann reaction conditions using $Zn(CN)_2$ and HCl [10].

Afromosin (**1a**) and cladrastin (**1b**) were synthesized via formylation of the corresponding 2-hydroxydeoxybenzoins **2a** and **2b** using Vilsmeier reagent (complex of DMF and $POCl_3$) in the presence of $Et_2O{\cdot}BF_3$ followed by heterocyclization. Reaction of starting 2-hydroxydeoxybenzoins **2a** and **2b** with an excess of acetic anhydride in the presence of Et_3N as the base produced 2-methyl-7-acetoxyisoflavones **3c** and **3d**. The 2-methyl derivatives of afromosin (**1c**) and cladrastin (**1d**) were synthesized via deacylation of 7-acetoxyisoflavones **3c** and **3d** in acidic solution.

Aminals of secondary amines are the most reactive aminomethylation reagents and were selected for studying features of Mannich reactions involving 7-hydroxy-6-methoxyisoflavonoids **1a**–**d** because the direction and sequence of aminomethylation of the isoflavonoid chromone core were practically independent of the aminomethylation reagent [20]. This could enable aminomethyl derivatives at all positions capable of undergoing electrophilic substitution to be obtained.

Thus, 7-hydroxyisoflavones **1a**–**d** reacted with an excess of the aminal in *i*-PrOH to form the 8-aminomethyl derivatives. The yields of the target Mannich bases **4b**–**d**, **5a**–**d**, **6a**, and **7a**–**d** were slightly reduced as compared with those of the aminomethyl derivatives of other 7-hydroxyisoflavones because of the discordant orientation of the hydroxyl and methoxyl in isoflavone ring A. Thus, the yields of Mannich bases of **1a** and **1b** and their 2-methyl derivatives were 69–90%. Increasing the amount of aminal or using the higher boiling solvent dioxane did not significantly affect the yields of the 8-aminomethyl derivatives.



5a-d: R_3 = H, **6a:** R_3 = OH

a: $R_1 = R_2$ = H; **b:** R_1 = H, R_2 = OMe; **c:** R_1 = Me, R_2 = H; **d:** R_1 = Me, R_2 = OMe

a. Bis(dimethylamino)methane, 1,12-methylenedi(3-*R*-piperidine) or 1,12-methylenebis(4-methylpiperazine), *i*-PrOH

The structures of **4b**–**d**, **5a**–**d**, **6a**, and **7a**–**d** were confirmed by NMR spectroscopy. PMR spectra of the aminomethyl derivatives exhibited proton resonances for the isoflavone and amine fragments, lacked a resonance for H-8, and showed a 2H singlet for the methylene at 3.98–4.07 ppm.

EXPERIMENTAL

The course of reactions and purity of products were monitored by TLC on Merck plates (Germany) using CH_2Cl_2–MeOH (100:1, 50:1) and EtOAc. PMR and ^{13}C NMR spectra were measured vs. TMS internal standard on the δ-scale on Varian-400 (400 and 100 MHz) and Varian 500 instruments (500 and 125 MHz). GC-MS were recorded using an Agilent 1100 Series HPLC-MS equipped with an Agilent LC\MSD SL mass-selective diode-array detector and chemical ionization at atmospheric pressure (APCI). Elemental analyses of all compounds agreed with those calculated.

General Method for Preparing 2-Aryl-1-(2,4-dihydroxy-5-methoxyphenyl)ethanones 2a and 2b. A solution of arylacetonitrile (10 mmol) and 4-methoxyresorcinol (100 mmol) in $Et_2O{\cdot}BF_3$ (50 mL) was stirred, purged with a stream of dry

HCl for 5–6 h, left overnight, transferred into hot H_2O (400 mL) containing conc. H_2SO_4 (10 mL), refluxed for 1.5–2 h, and cooled. The resulting precipitate was filtered off and crystallized from EtOH.

1-(2,4-Dihydroxy-5-methoxyphenyl)-2-(4-methoxyphenyl)ethanone (2a). $C_{16}H_{16}O_5$, yield 58%, mp 122–124°C. MS (CI): 289.0 $[M + H]^+$ (100). ^1H NMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 3.72, 3.78 (3H each, s, 5, 4′-OCH_3), 4.25 (2H, s, CH_2), 6.34 (1H, s, H-3), 6.88 (2H, d, J = 8.1, H-3′, 5′), 7.22 (2H, d, J = 8.1, H-2′, 6′), 7.43 (1H, s, H-6), 10.52 (1H, s, 4-OH), 12.37 (1H, s, 2-OH). ^{13}C NMR spectrum (100 MHz, DMSO-d_6, δ, ppm): 43.6, 55.0, 56.4, 103.3, 110.4, 113.4, 113.9, 127.2, 130.6, 141.1, 155.6, 158.0, 159.3, 202.0.

1-(2,4-Dihydroxy-5-methoxyphenyl)-2-(3,4-dimethoxyphenyl)ethanone (2b). $C_{17}H_{18}O_6$, yield 51%, mp 163–165°C. MS (CI): 319.0 $[M + H]^+$ (100). ^1H NMR spectrum (400 MHz, DMSO-d_6, δ, ppm): 3.74, 3.75, 3.78 (3H each, s, 6, 3′, 4′-OCH_3), 4.16 (2H, s, CH_2), 6.26 (1H, s, H-3), 6.77–6.85 (2H, m, H-5′, 6′), 6.87–6.91 (1H, m, H-2′), 7.35 (1H, s, H-6), 10.26 (1H, s, 4-OH), 12.37 (1H, s, 2-OH). ^{13}C NMR spectrum (125 MHz, $CDCl_3$, δ, ppm): 44.1, 55.5, 55.5, 56.4, 103.4, 110.5, 111.9, 113.4, 113.4, 121.6, 127.7, 141.1, 147.7, 148.7, 155.6, 159.4, 201.9.

General Method for Preparing 3-Aryl-7-hydroxy-6-methoxy-4*H*-chromen-4-ones 1a and 1b. A solution of **2a** or **2b** (10 mmol) in DMF (15 mL) was stirred, treated dropwise with $Et_2O{\cdot}BF_3$ (3.8 mL, 30 mmol) and then $POCl_3$ (2.3 mL, 25 mmol) at a rate such that the temperature did not rise above 70–75°C, held for 1 h at 75°C, poured into H_2O (200 mL), and heated at 90–95°C for 0.5 h. The isoflavone precipitate was filtered off and crystallized from EtOH.

7-Hydroxy-6-methoxy-3-(4-methoxyphenyl)-4*H*-chromen-4-one (1a). $C_{17}H_{14}O_5$, yield 69%, mp 225–226°C. MS (CI): 299.1 $[M + H]^+$ (100%). ^1H NMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 3.78, 3.87 (3H each, s, 6, 4′-OCH_3), 6.93 (1H, s, H-8), 6.98 (2H, d, J = 8.8, H-3′, 5′), 7.42 (1H, s, H-5), 7.51 (2H, d, J = 8.8, H-2′, 6′), 8.31 (1H, s, H-2). ^{13}C NMR spectrum (100 MHz, DMSO-d_6, δ, ppm): 55.1, 55.8, 102.8, 104.7, 113.6, 116.2, 122.6, 124.5, 130.1, 147.0, 151.7, 152.8, 152.9, 158.9, 174.2.

7-Hydroxy-3-(3,4-dimethoxyphenyl)-6-methoxy-4*H*-chromen-4-one (1b). $C_{18}H_{16}O_6$, yield 56%, mp 197–198°C. MS (CI): 329.2 $[M + H]^+$ (100%). ^1H NMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 3.78, 3.88 (6H, 3H, 2s, 6, 3′, 4′-OCH_3), 6.94 (1H, s, H-8), 7.00 (1H, d, J = 8.2, H-5′), 7.13 (1H, dd, J = 8.2, 2.0, H-6′), 7.20 (1H, d, J = 2.1, H-2′), 7.44 (1H, s, H-5), 8.36 (1H, s, H-2), 10.67 (1H, s, 7-OH). ^{13}C NMR spectrum (100 MHz, DMSO-d_6, δ, ppm): 55.5, 55.6, 55.8, 102.8, 104.7, 111.5, 112.8, 116.3, 121.1, 122.7, 124.8, 147.0, 148.3, 148.5, 151.7, 152.9, 153.0, 174.2.

General Method for Preparing 3-Aryl-2-methyl-6-methoxy-4-oxo-4*H*-chromen-7-yl Acetates 3c and 3d. A mixture of **2a** or **2b** (10 mmol), acetic anhydride (4.6 mL, 50 mmol), and Et_3N (5.6 mL, 40 mmol) was heated at 120–130°C for 6–10 h (TLC monitoring), and transferred into cold H_2O (100 mL) containing HCl (5 mL). The precipitate of isoflavone **3c** or **3d** was filtered off and crystallized from *i*-PrOH.

2-Methyl-6-methoxy-3-(4-methoxyphenyl)-4-oxo-4*H*-chromen-7-yl Acetate (3c). $C_{20}H_{18}O_6$, yield 87%, mp 174–175°C. MS (CI): 355.1 $[M + H]^+$ (100%). ^1H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.31, 2.38 (3H each, s, CH_3-2, 7-$OOCCH_3$), 3.85, 3.92 (3H each, s, 6, 4′-OCH_3), 6.98 (2H, d, J = 8.8, H-3′, 5′), 7.21 (1H, s, H-8), 7.21 (2H, d, J = 8.8, H-2′, 6′), 7.68 (1H, s, H-5). ^{13}C NMR spectrum (125 MHz, $CDCl_3$, δ, ppm): 19.5, 20.6, 55.2, 56.4, 106.6, 112.4, 113.8, 121.8, 122.5, 125.1, 131.5, 144.4, 149.1, 150.1, 159.1, 163.3, 168.2, 176.0.

3-(3,4-Dimethoxyphenyl)-6-methoxy-2-methyl-4-oxo-4*H*-chromen-7-yl Acetate (3d). $C_{21}H_{20}O_7$, yield 78%, mp 173–174°C. MS (CI): 385.1 $[M + H]^+$ (100%). ^1H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.31, 2.37 (3H each, s, CH_3-2, 7-$OOCCH_3$), 3.88, 3.91, 3.91 (3H each, s, 6, 3′, 4′-OCH_3), 6.78–6.83 (2H, m, H-2′, 6′), 6.93 (1H, d, J = 8.6, H-5′), 7.20 (1H, s, H-8), 7.67 (1H, s, H-5). ^{13}C NMR spectrum (125 MHz, $CDCl_3$, δ, ppm): 19.6, 20.6, 55.9, 55.9, 56.4, 106.6, 111.2, 112.4, 113.7, 121.8, 122.8, 125.6, 144.5, 148.6, 148.8, 149.2, 150.2, 163.5, 168.3, 176.1.

General Method for Preparing 3-Aryl-7-hydroxy-2-methyl-6-methoxy-4*H*-chromen-4-ones 1c and 1d. A hot solution of **3c** or **3d** (10 mmol) in the minimal amount of EtOH was treated with HCl (0.5 mL) and refluxed for 1–2 h (TLC monitoring). The precipitate of **1c** or **1d** that formed on cooling was filtered off and rinsed with EtOH.

7-Hydroxy-2-methyl-6-methoxy-3-(4-methoxyphenyl)-4*H*-chromen-4-one (1c). $C_{19}H_{18}O_6$, yield 78%, mp 215–216°C. MS (CI): 343.2 $[M + H]^+$ (100%). ^1H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.29 (3H, s, CH_3-2), 3.84, 3.97 (3H each, s, 6, 4′-OCH_3), 6.93 (1H, s, H-8), 6.96 (2H, d, J = 8.6, H-3′, 5′), 7.21 (2H, d, J = 8.6, H-2′, 6′), 7.56 (1H, s, H-5). ^{13}C NMR spectrum (100 MHz, $CDCl_3$, δ, ppm): 19.6, 55.4, 56.5, 102.6, 104.9, 113.9, 116.7, 122.3, 125.6, 131.7, 145.4, 151.3, 152.2, 159.1, 162.8, 176.5.

7-Hydroxy-3-(3,4-dimethoxyphenyl)-2-methyl-6-methohxy-4*H*-chromen-4-one (1d). $C_{18}H_{16}O_5$, yield 81%, mp 179–180°C. MS (CI): 313.1 $[M + H]^+$ (100%). ^1H NMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.24 (3H, s, CH_3-2), 3.73, 3.79, 3.85 (3H each, s, 6, 3′, 4′-OCH_3), 6.78 (1H, dd, J = 8.2, 2.0, H-6′), 6.84 (1H, d, J = 2.0, H-2′), 6.90 (1H, s, H-8), 6.99

(1H, d, J = 8.2, H-5′), 7.34 (1H, s, H-5), 10.59 (1H, s, 7-OH). ^{13}C NMR spectrum (100 MHz, DMSO-d_6, δ, ppm): 19.2, 55.5, 55.5, 55.8, 102.6, 104.8, 111.4, 114.4, 115.2, 121.6, 122.8, 125.9, 146.6, 148.1, 148.2, 151.3, 152.7, 162.2, 174.6.

General Method for Preparing Aminomethyl Derivatives 4–7. A hot solution of the appropriate isoflavone **1a**–**d** (2 mmol) in *i*-PrOH (20 mL) was treated with the corresponding aminal (2.2 mmol), refluxed for 3–5 h, and cooled (TLC monitoring). The solvent was evaporated *in vacuo*. The solid was triturated with Et_2O, dried, and crystallized from *i*-PrOH–hexane.

7-Hydroxy-8-[(dimethylaminomethyl)methyl]-3-(3,4-dimethoxyphenyl)-6-methoxy-4*H*-chromen-4-one (4b). $C_{21}H_{23}NO_6$, yield 79%, mp 169–170°C. MS (CI): 386.1 $[M + H]^+$ (100%). ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.46 (6H, s, $N(CH_3)_2$), 3.91, 3.93, 3.97 (3H each, s, 6, 3′, 4′-OCH_3), 4.02 (2H, s, CH_2-8), 6.93 (1H, d, J = 8.2, H-5′), 7.04 (1H, dd, J = 8.2, 2.1, H-6′), 7.25 (1H, d, J = 2.2, H-2′), 7.59 (1H, s, H-5), 7.93 (1H, s, H-2). ^{13}C NMR spectrum (125 MHz, $CDCl_3$, δ, ppm): 44.3, 55.1, 55.7, 55.7, 55.9, 103.8, 107.5, 110.9, 112.4, 115.8, 120.7, 123.6, 124.8, 146.8, 148.4, 148.7, 149.7, 151.1, 154.7, 175.3.

7-Hydroxy-8-[(dimethylaminomethyl)methyl]-2-methyl-6-methoxy-3-(4-methoxyphenyl)-4*H*-chromen-4-one (4c). $C_{21}H_{23}NO_5$, yield 81%, mp 108–109°C. MS (CI): 370.0 $[M + H]^+$ (100%). ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.30 (3H, s, CH_3-2), 2.46 (6H, s, $N(CH_3)_2$), 3.85, 3.95 (3H each, s, 6, 4′-OCH_3), 4.01 (2H, s, CH_2-8), 6.97 (2H, d, J = 8.8, H-3′, 5′), 7.21 (2H, d, J = 8.8, H-2′, 6′), 7.52 (1H, s, H-5′). ^{13}C NMR spectrum (100 MHz, $CDCl_3$, δ, ppm): 19.4, 44.6, 55.3, 55.5, 56.1, 104.3, 107.5, 113.8, 115.0, 122.2, 125.6, 131.6, 146.6, 149.5, 154.3, 159.0, 161.5, 176.3.

7-Hydroxy-8-[(dimethylaminomethyl)methyl]-3-(3,4-dimethoxyphenyl)-6-methoxy-2-methyl-4*H*-chromen-4-one (4d). $C_{22}H_{25}NO_6$, yield 89%, mp 176–177°C. MS (CI): 400.2 $[M + H]^+$ (100%). ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.30 (3H, s), 2.46 (6H, s, $N(CH_3)_2$), 3.87 (3H, s), 3.91 (3H, s), 3.95 (3H, s), 4.01 (2H, s, CH_2-8), 6.81 (1H, dd, J = 8.1, 2.0, H-6′), 6.83 (1H, d, J = 2.0, H-2′), 6.93 (1H, d, J = 8.1, H-5′), 7.52 (1H, s). ^{13}C NMR spectrum (125 MHz, $CDCl_3$, δ, ppm): 19.5, 44.6, 55.5, 55.9, 56.1, 104.3, 107.6, 111.2, 113.8, 115.1, 122.4, 122.9, 126.1, 146.7, 148.5, 148.7, 149.5, 154.4, 161.7, 176.3.

7-Hydroxy-6-methoxy-3-(4-methoxyphenyl)-8-(piperidin-1-ylmethyl)-4*H*-chromen-4-one (5a). $C_{23}H_{25}NO_5$, yield 80%, mp 176–177°C. MS (CI): 396.1 $[M + H]^+$ (100%). ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.37–1.58 (2H, m, H-4″), 1.60–1.73 (4H, m, H-3″, 5″), 2.39–2.93 (4H, m, H-2″, 6″), 3.79, 3.94 (3H each, s, 6, 4′-OCH_3), 3.98 (2H, s, CH_2-8), 6.92 (2H, d, J = 8.6, H-3′, 5′), 7.46 (2H, d, J = 8.6, H-2′, 6′), 7.52 (1H, s, H-5), 7.83 (1H, s, H-2), 12.71 (1H, s, 7-OH). ^{13}C NMR spectrum (125 MHz, $CDCl_3$, δ, ppm): 23.7, 25.7, 54.1, 54.9, 55.4, 56.2, 104.0, 107.2, 114.0, 116.0, 124.0, 124.7, 130.2, 147.0, 150.2, 151.1, 155.0, 159.5, 175.6.

7-Hydroxy-3-(3,4-dimethoxyphenyl)-6-methoxy-8-(piperidin-1-ylmethyl)-4*H*-chromen-4-one (5b). $C_{24}H_{27}NO_6$, yield 69%, mp 175–176°C. MS (CI): 426.1 $[M + H]^+$ (100%). ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.43–1.66 (2H, m, H-4″), 1.64–1.79 (4H, m, H-3″, 5″), 2.36–3.08 (4H, m, H-2″, 6″), 3.92, 3.93, 3.98 (3H each, s, 6, 3′, 4′-OCH_3), 4.03 (2H, s, CH_2-8), 6.93 (1H, d, J = 8.4, H-5′), 7.04 (1H, dd, J = 8.4, 2.0, H-6′), 7.26 (1H, d, J = 2.1, H-2′), 7.57 (1H, s, H-5), 7.92 (1H, s, H-2). ^{13}C NMR spectrum (100 MHz, $CDCl_3$, δ, ppm): 23.6, 25.6, 53.9, 54.8, 55.9, 56.0, 103.8, 107.1, 111.0, 112.5, 115.8, 120.8, 123.8, 125.0, 147.0, 148.6, 148.8, 150.0, 151.2, 155.1, 175.5.

7-Hydroxy-2-methyl-6-methoxy-3-(4-methoxyphenyl)-8-(piperidin-1-ylmethyl)-4*H*-chromen-4-one (5c). $C_{24}H_{27}NO_5$, yield 81%, mp 186–187°C. MS (CI): 410.1 $[M + H]^+$ (100%). ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.48–1.65 (2H, m, H-4″), 1.66–1.81 (4H, m, H-3″, 5″), 2.28 (3H, s, CH_3-2), 2.53–2.82 (4H, m, H-2″, 6″), 3.84, 3.95 (3H each, s, 6, 4′-OCH_3), 4.02 (2H, s, CH_2-8), 6.96 (2H, d, J = 8.6, H-3′, 5′), 7.20 (2H, d, J = 8.6, H-2′, 6′), 7.49 (1H, s, H-5). ^{13}C NMR spectrum (100 MHz, $CDCl_3$, δ, ppm): 19.3, 23.6, 25.6, 54.0, 54.9, 55.2, 56.0, 104.0, 106.9, 113.7, 114.8, 122.1, 125.6, 131.6, 146.5, 149.6, 154.5, 158.9, 161.3, 176.2.

7-Hydroxy-3-(3,4-dimethoxyphenyl)-2-methyl-6-methoxy-8-(piperidin-1-ylmethyl)-4*H*-chromen-4-one (5d). $C_{25}H_{29}NO_6$, yield 75%, mp 203–204°C. MS (CI): 440.1 $[M + H]^+$ (100%). ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.41–1.64 (2H, m, H-4″), 1.63–1.79 (4H, m, H-3″, 5″), 2.30 (3H, s, CH_3-2), 2.49–2.90 (4H, m, H-2″, 6″), 3.88, 3.92, 3.95 (3H each, s, 6, 3′, 4′-OCH_3), 4.03 (2H, s, CH_2-8), 6.81 (1H, dd, J = 8.1, 1.9, H-6′), 6.84 (1H, d, J = 1.9, H-2′), 6.93 (1H, d, J = 8.2, H-5′), 7.50 (1H, s, H-5). ^{13}C NMR spectrum (125 MHz, $CDCl_3$, δ, ppm): 19.2, 23.5, 25.5, 53.8, 54.7, 55.7, 55.8, 103.7, 106.8, 110.9, 113.6, 114.6, 122.1, 122.6, 125.9, 146.4, 148.2, 148.4, 149.5, 154.4, 161.4, 176.0.

7-Hydroxy-8-[(3-hydroxypiperidin-1-yl)methyl]-6-methoxy-3-(4-methoxyphenyl)- 4*H*-chromen-4-one (6a). $C_{23}H_{25}NO_6$, yield 90%, mp 175–176°C. MS (CI): 412.1 $[M + H]^+$ (100%). ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.40–1.74, 1.86–1.98, 2.26–2.53, 2.70–2.84, 2.91–3.03, 3.89–3.95 (2H, 3H, 2H, 1H, 1H, 1H, 6m, piperidine), 3.84, 3.97 (3H each, s, 6, 4′-OCH_3), 4.06 (2H, s, CH_2-8), 6.97 (2H, d, J = 8.6, H-3′, 5′), 7.50 (2H, d, J = 8.6, H-2′, 6′), 7.58 (1H, s, H-5), 7.89 (1H, s, H-2). ^{13}C NMR spectrum (125 MHz, $CDCl_3$, δ, ppm): 22.3, 32.1, 53.0, 54.3, 55.4, 56.2, 60.0, 66.4, 104.2, 107.3, 114.0, 116.2, 124.0, 124.6, 130.2, 147.0, 150.1, 151.2, 154.7, 159.5, 175.7.

7-Hydroxy-8-[(4-methylpiperazin-1-yl)methyl]-6-methoxy-3-(4-methoxyphenyl)-4*H*-chromen-4-one (7a). $C_{23}H_{26}N_2O_5$, yield 78%, mp 184–185°C. MS (CI): 411.1 $[M + H]^+$ (100%). ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.33 (3H, s, NCH_3), 2.40–3.01 (8H, m, piperazine ring), 3.85, 3.98 (3H each, s, 6, 4′-OCH_3), 4.07 (2H, s, CH_2-8), 6.97 (2H, d, J = 8.8, H-3′, 5′), 7.50 (2H, d, J = 8.8, H-2′, 6′), 7.59 (1H, s, H-5), 7.90 (1H, s, H-2). ^{13}C NMR spectrum (125 MHz, $CDCl_3$, δ, ppm): 45.9, 52.6, 53.9, 54.7, 55.3, 56.1, 104.2, 107.2, 113.9, 116.4, 123.9, 124.5, 130.1, 146.8, 149.9, 151.1, 154.0, 159.4, 175.5.

7-Hydroxy-3-(3,4-dimethoxyphenyl)-8-[(4-methylpiperazin-1-yl)methyl]-6-methoxy-4*H*-chromen-4-one (7b). $C_{24}H_{28}N_2O_6$, yield 80%, mp 198–200°C. MS (CI): 441.1 $[M + H]^+$ (100%). ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.33 (3H, s, NCH_3), 2.40–3.01 (8H, m, piperazine ring), 3.91, 3.93, 3.98 (3H each, s, 6, 3′, 4′-OCH_3), 4.07 (2H, s, CH_2-8), 6.93 (1H, d, J = 8.2, H-5′), 7.04 (1H, dd, J = 8.2, 2.0, H-6′), 7.25 (1H, d, J = 1.9, H-2′), 7.59 (1H, s, H-5), 7.94 (1H, s, H-2). ^{13}C NMR spectrum (125 MHz, $CDCl_3$, δ, ppm): 45.8, 52.6, 53.9, 54.7, 55.9, 56.1, 104.1, 107.2, 111.1, 112.5, 116.3, 120.8, 123.9, 124.9, 146.9, 148.6, 148.9, 149.9, 151.3, 154.1, 175.5.

7-Hydroxy-2-methyl-8-[(4-methylpiperazin-1-yl)methyl]-6-methoxy-3-(4-methoxyphenyl)-4*H*-chromen-4-one (7c). $C_{24}H_{28}N_2O_5$, yield 78%, mp 203–204°C. MS (CI): 425.2 $[M + H]^+$ (100%). ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.30, 2.33 (3H each, s, CH_3-2, NCH_3), 2.41–3.20 (8H, m, piperazine ring), 3.85, 3.96 (3H each, s, 6, 4′-OCH_3), 4.07 (2H, s, CH_2-8), 6.97 (2H, d, J = 8.8, H-3′, 5′), 7.21 (2H, d, J = 8.8, H-2′, 6′), 7.52 (1H, s, H-5). ^{13}C NMR spectrum (100 MHz, $CDCl_3$, δ, ppm): 19.3, 45.8, 52.6, 54.0, 54.7, 55.2, 56.0, 104.2, 106.9, 113.7, 115.2, 122.1, 125.5, 131.5, 146.4, 149.5, 153.6, 158.9, 161.5, 176.1.

7-Hydroxy-3-(3,4-dimethoxyphenyl)-2-methyl-8-[(4-methylpiperazin-1-yl)methyl]-6-methoxy-4*H*-chromen-4-one (7d). $C_{25}H_{30}N_2O_6$, yield 72%, mp 194–195°C. MS (CI): 455.2 $[M + H]^+$ (100%). ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.31, 2.32 (3H, s, CH_3-2, NCH_3), 2.42–3.04 (8H, m, piperazine ring), 3.87, 3.91, 3.95 (3H each, s, 6, 3′, 4′-OCH_3), 4.06 (2H, s, CH_2-8), 6.80 (1H, dd, J = 8.1, 1.9, H-6′), 6.83 (1H, d, J = 1.9, H-2′), 6.92 (1H, d, J = 8.1, H-5′), 7.51 (1H, s, H-5). ^{13}C NMR spectrum (125 MHz, $CDCl_3$, δ, ppm): 19.3, 45.7, 52.5, 53.8, 54.6, 55.7, 55.9, 104.1, 106.8, 110.9, 113.6, 115.0, 122.2, 122.6, 125.8, 146.3, 148.3, 148.5, 149.4, 153.6, 161.5, 176.0.

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