Chemistry of Natural Compounds, Vol. 49, No. 2, May, 2013 [Russian original No. 2, March–April, 2013]

SYNTHESIS AND AMINOMETHYLATION OF 7-HYDROXY-5-METHOXYISOFLAVONES

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UDC 547.814.5

A synthetic method for 7-hydroxy-5-methoxyisoflavones starting from 5,7-dihydroxyisoflavones was developed. Dimethylcarbamoylchloride was proposed for protection of the 7-hydroxy group. Aminomethylation of the synthesized 7-hydroxy-5-methoxyisoflavones by formaldehyde aminals was studied.

Keywords: 5,7-dihydroxyisoflavone, 7-hydroxy-5-methoxyisoflavone, biochanin A, 5-*O*-methylbiochanin A, aminomethylation.

Natural 4*H*-benzopyran-4-ones (chromones) occur more often than not as hydroxylated, methoxylated, and glycosylated derivatives, the overwhelming majority of which contain O atoms in resorcinol-like or phloroglucinol-like positions. 7-*O*-methyl derivatives are the most common monomethylated natural aglycons of chromones with the phloroglucinol structure whereas 7-hydroxy-5-*O*-methyl compounds are few and, as a rule, exist in minor amounts. Among them are maritimin (from *Pancratium maritimum*) [1], 5-*O*-methylchrysine (from a Uruguayan propolis) [2], 7-hydroxy-6,8-dimethyl-5-methoxyflavone and 7-hydroxy-6,8-dimethyl-5-methoxyisoflavone (from *Cleistocalyx operculatus*) [3], isoprunetin (from *Maackia amurensis*) [4], gerontoisoflavone A (from *Cudrania cochichinensis*) [5], and 5-*O*-methylbiochanin A (**5b**) (from *Echinospartum horridum*) [6]. However, the chemical synthesis of 7-hydroxy-5-methoxyflavonoids is poorly studied.

Natural derivatives of chromones containing a N atom are chromane alkaloids according to their biogenetic origin [7]. Among them, the most well-known is the alkaloid rohitukine, which was isolated from *Dysoxylum binectariferum* and contains a piperidine group [8]. Its synthetic derivative is known by the name "Flavopyridol" and is used for cancer therapy as an inhibitor of cyclin-dependent kinases (CDKs) [9]. Aminomethyl derivatives of flavones are also known to inhibit CDK-2. Several of them exhibit higher activity than Flavopyridol [10].

The goal of our work was to develop a synthetic method for 7-hydroxy-5-methoxyflavones and to study their aminomethylation in order to prepare isomers of the alkaloid buchenavianine, which was isolated from *Buchenavia capitata* [11].

As shown earlier, the reaction of chrysine (5,7-dihydroxyflavone) with equivalent amounts of amine and aldehyde or 2-hydroxypiperidine produced a mixture of 6- and 8-aminomethyl derivatives. Their ratio depended on the amine component and the reaction conditions [12]. We synthesized previously their 6,8-bisaminomethyl derivatives by using an excess of the aminal for aminomethylation of 5,7-dihydroxyisoflavones [13, 14].

8-Aminomethyl derivatives of 5,7-dimethoxy-2′-chloroflavone were synthesized by selective methylation of chalcone hydroxyl groups and subsequent aminomethylation and oxidative cyclization. However, the subsequent demethylation occurred only with formation of 5-hydroxy-7-methoxyflavone derivatives [10].

The direction of the aminomethylation depended strongly on the number of electron-donating groups, especially hydroxyls and methoxyls, located in the same core in the appropriate orientation. Unfortunately, no examples of aminomethylation of 5-hydroxy-7-methoxychromones or 7-hydroxy-5-methoxychromones are known.

Thus, we synthesized 2,4,6-trihydroxydeoxybenzoins **1a**–**e** via reaction of phloroglucinol with arylacetonitriles under Hoesch reaction conditions. These served as starting materials for the synthesis of natural 5,7-dihydroxyisoflavone (**2a**) [15], its halo-derivatives **2c** and **2d**, biochanin A (**2b**) [16], and its regioisomer **2e**. We used the method proposed by Bass to perform the cyclization [17].

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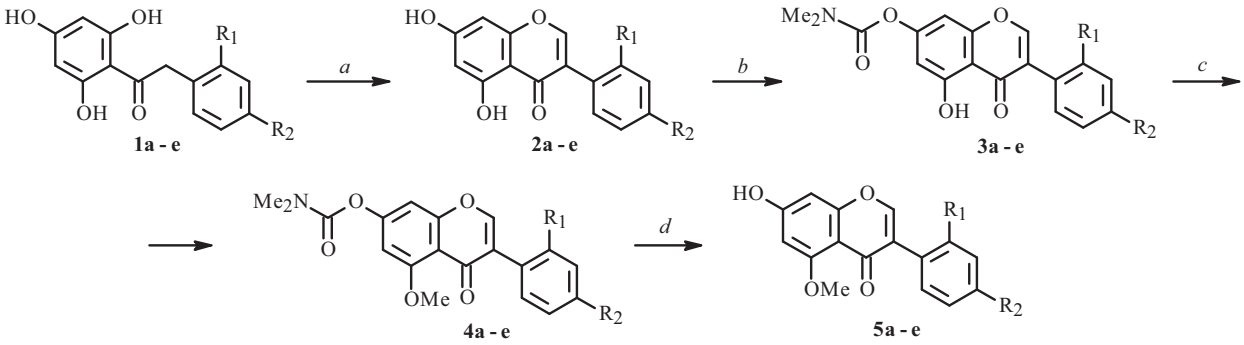


a: $R_1 = R_2 = H$; **b:** $R_1 = H$, $R_2 = OMe$; **c:** $R_1 = H$, $R_2 = F$; **d:** $R_1 = H$, $R_2 = Cl$; **e:** $R_1 = OMe$, $R_2 = H$

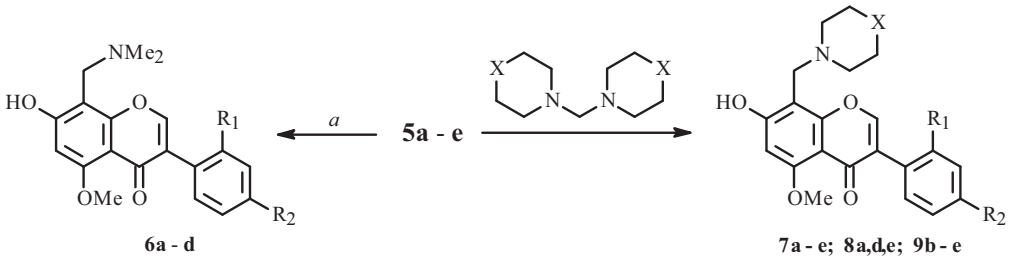
a. DMF, $MeSO_2Cl$; *b.* Me_2NCOCl, Py; *c.* Me_2SO_4; *d.* HCl

We proposed dimethylcarbamoylchloride in the presence of pyridine for protection of the 7-hydroxyl of the chromone ring. As it turned out, monoacylation of 5,7-dihydroxyisoflavones **2a**–**e** occurred upon prolonged storage of the reaction mixture at room temperature with practically quantitative yield of **3a**–**e**.

NMR spectra of **3a**–**e** contained resonances for the dimethylcarbamoyl group as two 3H singlets due to hindered rotation around the C(=O)N bond. However, the hydroxyl resonance was observed in the range 12.71–12.83 ppm. This was indicative of an intramolecular H-bond with the carbonyl.

Subsequent alkylation of **3a**–**e** by dimethylsulfate in Me_2CO in the presence of potash formed 7-*O*-protected 5-methoxyisoflavones **4a**–**e**. Their deacylation in acidic solution produced 7-hydroxy-5-methoxyisoflavones 5-*O*-methylbiochanin A (**5b**) and its analogs **5a**, **c**–**e**.

We studied the reaction of isoflavones **5a**–**e** with aminomethylating reagents such as a mixture of secondary amines and their hydrochlorides and formaldehyde in EtOH or dioxane in addition to aminals in organic solvents in order to synthesize the aminomethyl derivatives. We used EtOH, dioxane, and ethyleneglycol monomethyl ether as the reaction medium. As it turned out, the most convenient method for synthesizing isoflavone aminomethyl derivatives **5a**–**e** used aminals in anhydrous EtOH that could be synthesized by the reaction of amines with formalin. Monoaminomethyl derivatives **6**–**9** were formed in high yields under these conditions. As it turned out, the reaction occurred regioselectively if equivalent amounts or a significant excess of formaldehyde aminals were used. Exclusively monoaminomethyl derivatives were synthesized. However, aminomethylation of chrysine occurred with formation of a mixture of 6- and 8-aminomethyl derivatives [12]. 5,7-Dihydroxyisoflavone 6,8-bisaminomethyl derivatives were isolated if an excess of the aminomethylating reagent was used [13, 14].



a: $R_1 = R_2 = H$; **b:** $R_1 = H$, $R_2 = OMe$; **c:** $R_1 = H$, $R_2 = F$
d: $R_1 = H$, $R_2 = Cl$; **e:** $R_1 = OMe$, $R_2 = H$
7a - e: X = CH_2; **8a,d,e:** X = NMe; **9b - e:** X = O
a. $CH_2(NMe_2)_2$

PMR spectra of these compounds contained resonances for isoflavone and amine protons. The resonance of the Ar–CH_2–N protons was observed as a 2H singlet in the range 3.94–4.31 ppm. The structures of aminomethyl derivatives **6**–**9** were elucidated based on COSY and NOESY NMR spectra using **9b** as an example. Thus, the COSY NMR spectrum of **9b** exhibited cross-peaks of the 5-methoxy and a proton resonance at 6.36 ppm. This was indicative of the formation of 8-aminomethyl derivatives. Analogous positive cross-peaks were observed in the 2D NOESY spectrum. This was possible only if the aminomethylation occurred at the chromone 8-position.

Thus, we developed a synthetic method for 7-hydroxy-5-methoxyisoflavones that consisted of protection of the chromone 7-hydroxy group using dimethylcarbamoylchloride, methylation of the 5-hydroxy group, and subsequent deacylation

in acidic solution. Aminomethylation of 5-*O*-methylbiochanin A and its analogs containing two electron-donating groups in ring A was studied. Mannich reaction of 7-hydroxy-5-methoxyisoflavones aminomethylated them regioselectively in the chromone 8-position.

EXPERIMENTAL

The course of reactions and purity of products were monitored by TLC on plates (Merck, Germany) using $CHCl_3$:MeOH mixtures (9:1, 95:5) as eluent. PMR, COSY, and NOESY spectra were measured in DMSO-d_6 on the δ-scale relative to TMS (internal standard) on a Mercury M 400 instrument (Varian, 400 MHz). Elemental analyses of all compounds agreed with those calculated.

General Method for Preparing Aminals. The appropriate amine (2 mol) was cooled, stirred, treated with formaldehyde (100 mL, 37%) at 20–25°C, and treated with solid KOH until completely layered. The upper layer was separated, dried over KOH, and distilled at 15–20 mbar.

4,4′-Methylenedimorpholine. $C_6H_{18}N_2O_2$, yield 82%, bp 127–129°C (16 mbar) {lit. [18] bp 127–129°C (14 mbar)}. PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.36–2.53 (8H, m, $NC\underline{H}_2CH_2O$), 2.88 (2H, s, NCH_2N'), 3.60–3.73 (8H, m, $NCH_2C\underline{H}_2O$).

1,1′-Methylenedipiperidine. $C_{11}H_{22}N_2$, yield 89%, bp 117–118°C (15 mbar) {lit. [18] bp 110–111°C (11 mbar)}. PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.30–1.48 (4H, m, $NCH_2CH_2C\underline{H}_2$), 1.48–1.60 (8H, m, $NCH_2C\underline{H}_2CH_2$), 2.28–2.50 (8H, m, $NC\underline{H}_2CH_2CH_2$), 2.83 (2H, s, NCH_2N').

1,1′-Methylene Bis(4-methylpiperazine). $C_{11}H_{24}N_4$, yield 84%, bp 143–145°C (20 mbar) {lit. [19] bp 140°C (12 mbar)}. PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.25 (6H, s, NCH_3), 2.26–2.75 (16H, m, $NC\underline{H}_2C\underline{H}_2NCH_3$), 2.89 (2H, s, NCH_2N').

General Method for Preparing Ketones 1a–e. A solution of arylacetonitrile (100 mmol) in anhydrous Et_2O (50 mL) was cooled, stirred, purged for 2–4 h with a stream of dry HCl until the mixture was saturated, treated with a suspension of phloroglucinol (100 mmol) and freshly fused $ZnCl_2$ (10 mmol) in anhydrous Et_2O (50 mL), stirred, purged for 4–6 h with a stream of dry HCl, and left overnight. The precipitated ketimine was filtered and hydrolyzed by dissolving in hot water (200 mL) containing conc. H_2SO_4 (5 mL), refluxing for 1.5–2 h, and cooling. The resulting precipitate was filtered off and crystallized from MeOH.

1-(2,4,6-Trihydroxyphenyl)-2-phenylethanone (1a). $C_{14}H_{12}O_4$, yield 59%, mp 163–164°C (lit. [20] mp 164°C). PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 4.35 (2H, s, $COCH_2$), 5.83 (2H, s, H-3, H-5), 7.18–7.25 (3H, m, H-2′, H-4′, H-6′), 7.26–7.32 (2H, m, H-3′, H-5′), 10.51 (1H, s, 4-OH), 12.24 (2H, s, 2-OH, 6-OH).

2-(4-Methoxyphenyl)-1-(2,4,6-trihydroxyphenyl)ethanone (1b). $C_{15}H_{14}O_5$, yield 74%, mp 183–185°C (lit. [20] mp 184–185°C). PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 3.72 (3H, s, 4′-OCH_3), 4.26 (2H, s, $COCH_2$), 5.82 (2H, s, H-3, H-5), 6.85 (2H, d, ^3J = 8.8, H-3′, H-5′), 7.14 (2H, d, ^3J = 8.8, H-2′, H-6′), 10.41 (1H, s, 4-OH), 12.25 (2H, s, 2-OH, 6-OH).

1-(2,4,6-Trihydroxyphenyl)-2-(4-fluorophenyl)ethanone (1c). $C_{14}H_{11}FO_4$, yield 53%, mp 198–200°C (lit. [21] mp 199–200°C). PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 4.34 (2H, s, $COCH_2$), 5.83 (2H, s, H-3, H-5), 7.11 (2H, dd, $^3J_{HH}$ = 8.8, $^3J_{HF}$ = 8.8, H-3′, H-5′), 7.25 (2H, dd, $^3J_{HH}$ = 8.8, $^4J_{HF}$ = 5.8, H-2′, H-6′), 10.43 (1H, s, 4-OH), 12.23 (2H, s, 2-OH, 6-OH).

1-(2,4,6-Trihydroxyphenyl)-2-(4-chlorophenyl)ethanone (1d). $C_{14}H_{11}ClO_4$, yield 91%, mp 222–224°C (lit. [21] mp 221–222°C). PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 4.35 (2H, s, $COCH_2$), 5.83 (2H, s, H-3, H-5), 7.24 (2H, d, ^3J = 8.2, H-3′, H-5′), 7.35 (2H, d, ^3J = 8.2, H-2′, H-6′), 10.41 (1H, s, 4-OH), 12.28 (2H, s, 2-OH, 6-OH).

2-(2-Methoxyphenyl)-1-(2,4,6-trihydroxyphenyl)ethanone (1e). $C_{15}H_{14}O_5$, yield 63%, mp 172–174°C (lit. [22] mp 172°C). PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 3.71 (3H, s, 2′-OCH_3), 4.29 (2H, s, $COCH_2$), 5.85 (2H, s, H-3, H-5), 6.84–6.91 (1H, m, H-5′), 6.94–6.98 (1H, m, H-3′), 7.08–7.12 (1H, m, H-6′), 7.19–7.27 (1H, m, H-4′), 10.38 (1H, s, 4-OH), 12.19 (2H, s, 2-OH, 6-OH).

General Method for Preparing 5,7-Dihydroxyisoflavones 2a–e. A solution of the appropriate compound **1a–e** (10 mmol) in DMF (10 mL) was treated with $BF_3 \cdot Et_2O$ (40 mmol) and methanesulfonylchloride (30 mmol) at a rate such that the temperature of the reaction mixture did not rise above 50°C, stirred and heated at 100°C for 3–4 h, and hydrolyzed by pouring into cold H_2O (100 mL). After hydrolysis, compounds **2a–e** were filtered off and crystallized from MeOH.

5,7-Dihydroxy-3-phenyl-4*H*-chromen-4-one (2a). $C_{15}H_{10}O_4$, yield 77%, mp 199–201°C (lit. [17] mp 198–201°C, [23] 200–201°C). PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 6.24 (1H, d, ^4J = 2.0, H-8), 6.40 (1H, d, ^4J = 2.0, H-6), 7.36–7.47 (3H, m, H-2′, H-4′, H-6′), 7.54–7.58 (2H, m, H-3′, H-5′), 8.41 (1H, s, H-2), 10.97 (1H, s, 7-OH), 12.89 (1H, s, 5-OH).

5,7-Dihydroxy-3-(4-methoxyphenyl)-4*H*-chromen-4-one (2b). $C_{16}H_{12}O_5$, yield 71%, mp 214–216°C (lit. [17] mp 211–213°C). PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 3.79 (3H, s, 4′-OCH_3), 6.23 (1H, d, ^4J = 2.0, H-8), 6.39 (1H, d, ^4J = 2.0, H-6), 7.00 (2H, d, ^3J = 8.8, H-3′, H-5′), 7.50 (2H, d, ^3J = 8.8, H-2′, H-6′), 8.37 (1H, s, H-2), 10.91 (1H, s, 7-OH), 12.93 (1H, s, 5-OH).

5,7-Dihydroxy-3-(4-fluorophenyl)-4*H*-chromen-4-one (2c). $C_{15}H_9FO_4$, yield 90%, mp 223–225°C (lit. [17] mp 225–226°C). PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 6.24 (1H, d, ^4J = 2.2, H-8), 6.41 (1H, d, ^4J = 2.2, H-6), 7.28 (2H, dd, $^3J_{HH}$ = 8.8, $^3J_{HF}$ = 8.8, H-3′, H-5′), 7.61 (2H, dd, $^3J_{HH}$ = 8.8, $^4J_{HF}$ = 5.7, H-2′, H-6′), 8.43 (1H, s, H-2), 10.97 (1H, s, 7-OH), 12.83 (1H, s, 5-OH).

5,7-Dihydroxy-3-(4-chlorophenyl)-4*H*-chromen-4-one (2d). $C_{15}H_9ClO_4$, yield 90%, mp 233–235°C (lit. [21] 236–237°C). PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 6.25 (1H, d, ^4J = 2.0, H-8), 6.41 (1H, d, ^4J = 2.0, H-6), 7.51 (2H, d, ^3J = 8.1, H-3′, H-5′), 7.60 (2H, dd, ^3J = 8.1, H-2′, H-6′), 8.47 (1H, s, H-2), 10.97 (1H, s, 7-OH), 12.80 (1H, s, 5-OH).

5,7-Dihydroxy-3-(2-methoxyphenyl)-4*H*-chromen-4-one (2e). $C_{16}H_{12}O_5$, yield 79%, mp 200–201°C. PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 3.74 (3H, s, 2′-OCH_3), 6.24 (1H, d, ^4J = 2.0, H-8), 6.41 (1H, d, ^4J = 2.0, H-6), 6.98–7.03 (1H, m, H-5′), 7.07–7.11 (1H, m, H-3′), 7.23–7.27 (1H, m, H-6′), 7.37–7.43 (1H, m, H-4′), 8.24 (1H, s, H-2), 10.92 (1H, s, 7-OH), 12.86 (1H, s, 5-OH).

General Method for Preparing 5-Hydroxy-7-dimethylcarbamoylisoflavones 3a–e. A solution of 5,7-dihydroxyisoflavone **2a–e** (10 mmol) in the minimum volume of anhydrous Py was cooled, stirred, treated with dimethylcarbamoylchloride (11 mmol), left for 1 d, and poured into acidified H_2O (100 mL). The resulting precipitate was filtered off, dried, and crystallized from MeOH.

5-Hydroxy-4-oxo-3-phenyl-4*H*-chromen-7-yl dimethylcarbamate (3a). $C_{18}H_{15}NO_5$, yield 82%, mp 156–157°C. PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.94, 3.05 [each 3H, s, $(CH_3)_2$NCOO-7], 6.67 (1H, d, ^4J = 2.2, H-8), 6.99 (1H, d, ^4J = 2.2, H-6), 7.38–7.50 (3H, m, H-2′, H-4′, H-6′), 7.55–7.62 (2H, m, H-3′, H-5′), 8.58 (1H, s, H-2), 12.85 (1H, s, 5-OH).

5-Hydroxy-3-(4-methoxyphenyl)-4-oxo-4*H*-chromen-7-yl dimethylcarbamate (3b). $C_{19}H_{17}NO_6$, yield 78%, mp 149–150°C. PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.98, 3.10 [each 3H, s, $(CH_3)_2$NCOO-7], 3.82 (3H, s, 4′-OCH_3), 6.53 (1H, s, H-8), 6.79 (1H, s, H-6), 6.94 (2H, d, ^3J = 8.5, H-3′, H-5′), 7.48 (2H, d, ^3J = 8.5, H-2′, H-6′), 8.31 (1H, s, H-2), 12.83 (1H, s, 5-OH).

5-Hydroxy-4-oxo-3-(4-fluorophenyl)-4*H*-chromen-7-yl dimethylcarbamate (3c). $C_{18}H_{14}FNO_5$, yield 75%, mp 180–181°C. PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.93, 3.05 [each 3H, s, $(CH_3)_2$NCOO-7], 6.67 (1H, d, ^4J = 2.2, H-8), 6.98 (1H, d, ^4J = 2.2, H-6), 7.30 (2H, dd, $^3J_{HH}$ = 8.8, $^3J_{HF}$ = 8.8, H-3′, H-5′), 7.63 (2H, dd, $^3J_{HH}$ = 8.8, $^4J_{HF}$ = 5.6, H-2′, H-6′), 8.59 (1H, s, H-2), 12.79 (1H, s, 5-OH).

5-Hydroxy-4-oxo-3-(4-chlorophenyl)-4*H*-chromen-7-yl dimethylcarbamate (3d). $C_{18}H_{14}ClNO_5$, yield 72%, mp 186–187°C. PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.94, 3.05 [each 3H, s, $(CH_3)_2$NCOO-7], 6.66 (1H, d, ^4J = 2.0, H-8), 6.96 (1H, d, ^4J = 2.0, H-6), 7.51 (2H, d, ^3J = 8.5, H-3′, H-5′), 7.62 (2H, dd, ^3J = 8.5, H-2′, H-6′), 8.57 (1H, s, H-2), 12.71 (1H, s, 5-OH).

5-Hydroxy-3-(2-methoxyphenyl)-4-oxo-4*H*-chromen-7-yl dimethylcarbamate (3e). $C_{19}H_{17}NO_6$, yield 82%, mp 163–165°C. PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.94, 3.06 [each 3H, s, $(CH_3)_2$NCOO-7], 3.75 (3H, s, 2′-OCH_3), 6.68 (1H, d, ^4J = 2.0, H-8), 6.99 (1H, d, ^4J = 2.0, H-6), 7.00–7.05 (1H, m, H-5′), 7.10–7.14 (1H, m, H-3′), 7.26–7.31 (1H, m, H-6′), 7.39–7.46 (1H, m, H-4′), 8.42 (1H, s, H-2), 12.81 (1H, s, 5-OH).

General Method for Preparing 5-Methoxy-7-dimethylcarbamoylisoflavones 4a–e. A hot solution of the appropriate 5-hydroxyisoflavone **3a–e** (10 mmol) in anhydrous Me_2CO (50 mL) was treated with freshly calcined potash (30 mmol), stirred and refluxed, treated with dimethylsulfate (12 mmol), held for 6–8 h (end of reaction determined by TLC), and poured into acidified ice water (100 mL). The resulting precipitate was filtered off, dried, and crystallized from MeOH.

5-Methoxy-4-oxo-3-phenyl-4*H*-chromen-7-yl dimethylcarbamate (4a). $C_{19}H_{17}NO_5$, yield 71%, mp 126–127°C. PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.94, 3.07 [each 3H, s, $(CH_3)_2$NCOO-7], 3.85 (3H, s, 5-OCH_3), 6.83 (1H, d, ^4J = 2.0, H-8), 6.99 (1H, d, ^4J = 2.0, H-6), 7.33–7.44 (3H, m, H-2′, H-4′, H-6′), 7.48–7.53 (2H, m, H-3′, H-5′), 8.29 (1H, s, H-2).

5-Methoxy-3-(4-methoxyphenyl)-4-oxo-4*H*-chromen-7-yl dimethylcarbamate (4b). $C_{20}H_{19}NO_6$, yield 98%, mp 144–145°C. PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.94, 3.07 [each 3H, s, $(CH_3)_2NCOO$-7], 3.78 (3H, s, 4′-OCH_3), 3.85 (3H, s, 5-OCH_3), 6.82 (1H, d, ^4J = 2.4, H-8), 6.98 (2H, d, ^3J = 8.8, H-3′, H-5′), 6.99 (1H, d, ^4J = 2.4, H-6), 7.45 (2H, d, ^3J = 8.8, H-2′, H-6′), 8.26 (1H, s, H-2).

5-Methoxy-4-oxo-3-(4-fluorophenyl)-4*H*-chromen-7-yl dimethylcarbamate (4c). $C_{19}H_{16}FNO_5$, yield 73%, mp 153–155°C. PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 3.00, 3.12 [each 3H, s, $(CH_3)_2NCOO$-7], 3.91 (3H, s, 5-OCH_3), 6.69 (1H, d, ^4J = 1.7, H-8), 6.86 (1H, d, ^4J = 1.7, H-6), 7.13 (2H, dd, $^3J_{HH}$ = 8.8, $^3J_{HF}$ = 8.8, H-3′, H-5′), 7.52 (2H, dd, $^3J_{HH}$ = 8.8, $^4J_{HF}$ = 5.9, H-2′, H-6′), 8.11 (1H, s, H-2).

5-Methoxy-4-oxo-3-(4-chlorophenyl)-4*H*-chromen-7-yl dimethylcarbamate (4d). $C_{19}H_{16}ClNO_5$, yield 78%, mp 183–184°C. PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 3.01, 3.13 [each 3H, s, $(CH_3)_2NCOO$-7], 3.92 (3H, s, 5-OCH_3), 6.71 (1H, s, H-8), 6.87 (1H, s, H-6), 7.39 (2H, d, ^3J = 7.6, H-3′, H-5′), 7.52 (2H, d, ^3J = 7.6, H-2′, H-6′), 8.11 (1H, s, H-2).

5-Methoxy-3-(2-methoxyphenyl)-4-oxo-4*H*-chromen-7-yl dimethylcarbamate (4e). $C_{20}H_{19}NO_6$, yield 90%, mp 146–147°C. PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.95, 3.08 [each 3H, s, $(CH_3)_2NCOO$-7], 3.75 (3H, s, 2′-OCH_3), 3.83 (3H, s, 5-OCH_3), 6.82 (1H, d, ^4J = 2.2, H-8), 6.95–7.01 (2H, m, H-6, H-5′), 7.04–7.08 (1H, m, H-3′), 7.16–7.20 (1H, m, H-6′), 7.34–7.40 (1H, m, H-4′), 8.11 (1H, s, H-2).

General Method for Preparing 7-Hydroxy-5-methoxyisoflavones 5a–e. A solution of isoflavone **4a-e** (10 mmol) in ethyleneglycol monomethyl ether (20 mL) was treated with conc. HCl (2–3 mL), refluxed for 4–8 h (end of reaction determined by TLC), and poured into ice water (200 mL). The resulting precipitate was filtered off, dried, and crystallized from DMF:MeOH (1:1).

7-Hydroxy-5-methoxy-3-phenyl-4*H*-chromen-4-one (5a). $C_{16}H_{12}O_4$, yield 56%, mp 286–287°C. PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 3.85 (3H, s, 5-OCH_3), 6.34 (1H, s, H-8), 6.36 (1H, s, H-6), 7.27–7.40 (3H, m, H-2′, H-4′, H-6′), 7.42–7.51 (2H, m, H-3′, H-5′), 7.89 (1H, s, H-2), 10.30 (1H, s, 7-OH).

7-Hydroxy-5-methoxy-3-(4-methoxyphenyl)-4*H*-chromen-4-one (5b). $C_{17}H_{14}O_5$, yield 59%, mp 274–275°C (lit. [24] mp 294°C). PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 3.82 (3H, s, 4′-OCH_3), 3.85 (3H, s, 5-OCH_3), 6.34 (1H, s, H-8), 6.36 (1H, s, H-6), 6.86–6.95 (2H, m, H-3′, H-5′), 7.34–7.44 (2H, m, H-2′, H-6′), 7.85 (1H, s, H-2), 10.24 (1H, s, 7-OH).

7-Hydroxy-5-methoxy-3-(4-fluorophenyl)-4*H*-chromen-4-one (5c). $C_{16}H_{11}FO_4$, yield 47%, mp 292–293°C. PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 3.85 (3H, s, 5-OCH_3), 6.35 (1H, s, H-8), 6.37 (1H, s, H-6), 7.04–7.05 (2H, m, H-3′, H-5′), 7.45–7.55 (2H, m, H-2′, H-6′), 7.90 (1H, s, H-2), 10.19 (1H, s, 7-OH).

7-Hydroxy-5-methoxy-3-(4-chlorophenyl)-4*H*-chromen-4-one (5d). $C_{16}H_{11}ClO_4$, yield 53%, mp 283–284°C. PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 3.86 (3H, s, 5-OCH_3), 6.36 (1H, s, H-8), 6.37 (1H, s, H-6), 7.37 (2H, d, ^3J = 8.0, H-3′, H-5′), 7.51 (2H, d, ^3J = 8.0, H-2′, H-6′), 7.95 (1H, s, H-2), 10.28 (1H, s, OH-7).

7-Hydroxy-5-methoxy-3-(2-methoxyphenyl)-4*H*-chromen-4-one (5e). $C_{17}H_{14}O_5$, yield 61%, mp 290–292°C. PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 3.77 (3H, s, 2′-OCH_3), 3.84 (3H, s, 5-OCH_3), 6.34 (1H, s, H-8), 6.38 (1H, s, H-6), 6.91–7.02 (2H, m, H-3′, H-5′), 7.14–7.21 (1H, m, H-6′), 7.27–7.34 (1H, m, H-4′), 7.72 (1H, s, H-2), 10.16 (1H, s, 7-OH).

General Method for Aminomethylation of 7-Hydroxy-5-methoxyisoflavones 5a–e. A hot solution of the appropriate isoflavone **5a–e** (2 mmol) in anhydrous EtOH (20 mL) was treated with the appropriate aminal (2.2 mmol), refluxed for 3–5 h, and cooled (reaction monitored by TLC). The solvent was evaporated in *vacuo*. The solid was triturated with Et_2O, dried, and crystallized from *i*-PrOH:hexane. The reaction mixtures for **6b** and **6d** were treated with conc. HCl (1 mL), evaporated in vacuo, triturated with Et_2O, and crystallized from CH_3CN:MeOH (2:1).

7-Hydroxy-8-[(dimethylamino)methyl]-5-methoxy-3-phenyl-4*H*-chromen-4-one (6a). $C_{19}H_{19}NO_4$, yield 56%, mp 208–209°C. PMR spectrum (400 MHz, $CDCl_3$, δ, ppm): 2.43 [6H, s, $(CH_3)_2N$], 3.91 (2H, s, 8-CH_2), 3.92 (3H, s, 5-OCH_3), 6.35 (1H, s, H-6), 7.31–7.44 (3H, m, H-2′, H-4′, H-6′), 7.49–7.56 (2H, m, H-3′, H-5′), 7.75 (1H, s, H-2), 10.37 (1H, s, 7-OH).

7-Hydroxy-8-[(dimethylamino)methyl]-5-methoxy-3-(4-methoxyphenyl)-4*H*-chromen-4-one Hydrochloride (6b). $C_{20}H_{21}NO_5$·HCl, yield 54%, mp 180–181°C. PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.74 [6H, d, ^3J = 4.4, $(CH_3)_2N$], 3.79 (3H, s, 4′-OCH_3), 3.83 (3H, s, 5-OCH_3), 4.31 (2H, d, ^3J = 4.4, 8-CH_2), 6.67 (1H, s, H-6), 6.97 (2H, d, ^3J = 8.5, H-3′, H-5′), 7.43 (2H, d, ^3J = 8.5, H-2′, H-6′), 8.13 (1H, s, H-2), 10.13 (1H, m, NH^+), 11.84 (1H, s, 7-OH).

7-Hydroxy-8-[(dimethylamino)methyl]-5-methoxy-3-(4-fluorophenyl)-4*H*-chromen-4-one (6c). $C_{19}H_{18}FNO_4$, yield 73%, mp 210–211°C. PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.43 [6H, s, $(CH_3)_2N$], 3.84 (2H, s, 8-CH_2), 3.93 (3H, s, 5-OCH_3), 6.34 (1H, s, H-6), 7.08 (2H, dd, $^3J_{HH}$ = 8.8, $^3J_{HF}$ = 8.8, H-3′, H-5′), 7.36 (2H, dd, $^3J_{HH}$ = 8.8, $^4J_{HF}$ = 5.5, H-2′, H-6′), 7.74 (1H, s, H-2), 10.12 (1H, s, 7-OH).

7-Hydroxy-8-[(dimethylamino)methyl]-5-methoxy-3-(4-chlorophenyl)-4*H*-chromen-4-one Hydrochloride (6d). $C_{19}H_{18}ClNO_4 \cdot HCl$, yield 36%, mp 197–198°C. PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.77 [6H, d, ^3J = 4.4, $(CH_3)_2N$], 3.82 (3H, s, 5-OCH_3), 4.30 (2H, d, ^3J = 4.4, 8-CH_2), 6.72 (1H, s, H-8), 7.46–7.55 (4H, m, H-2′, H-3′, H-5′, H-6′), 8.26 (1H, s, H-2), 9.97 (1H, m, NH^+), 11.91 (1H, s, 7-OH).

7-Hydroxy-5-methoxy-8-(piperidin-1-ylmethyl)-3-phenyl-4*H*-chromen-4-one (7a). $C_{22}H_{23}NO_4$, yield 51%, mp 184–185°C. PMR spectrum (400 MHz, $CDCl_3$, δ, ppm): 1.17–3.55 (10H, m, piperidine protons), 3.79 (3H, s, 5-OCH_3), 4.11 (2H, s, 8-CH_2), 6.51 (1H, s, H-6), 7.28–7.38 (3H, m, H-2′, H-4′, H-6′), 7.43-7.47 (2H, m, H-3′, H-5′), 7.73 (1H, s, H-2).

7-Hydroxy-5-methoxy-3-(4-methoxyphenyl)-8-(piperidin-1-ylmethyl)-4*H*-chromen-4-one (7b). $C_{23}H_{25}NO_5$, yield 51%, mp 189–190°C. PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.17–3.33 (10H, m, piperidine protons), 3.83 (3H, s, 4′-OCH_3), 3.89 (2H, s, 8-CH_2), 3.92 (3H, s, 5-OCH_3), 6.31 (1H, s, H-6), 6.93 (2H, d, ^3J = 8.5, H-3′, H-5′), 7.47 (2H, d, ^3J = 8.5, H-2′, H-6′), 7.72 (1H, s, H-2), 9.05 (1H, s, 7-OH).

7-Hydroxy-5-methoxy-8-(piperidin-1-ylmethyl)-3-(4-fluorophenyl)-4*H*-chromen-4-one (7c). $C_{22}H_{22}FNO_4$, yield 53%, mp 197–198°C. PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.44–3.25 (10H, m, piperidine protons), 3.89 (3H, s, 5-OCH_3), 3.98 (2H, s, 8-CH_2), 6.40 (1H, s, H-6), 7.08 (2H, dd, $^3J_{HH}$ = 8.8, $^3J_{HF}$ = 8.8, H-3′, H-5′), 7.50 (2H, dd, $^3J_{HH}$ = 8.8, $^4J_{HF}$ = 5.5, H-2′, H-6′), 7.73 (1H, s, H-2).

7-Hydroxy-5-methoxy-8-(piperidin-1-ylmethyl)-3-(4-chlorophenyl)-4*H*-chromen-4-one (7d). $C_{22}H_{22}ClNO_4$, yield 62%, mp 212–213°C. PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.19–3.35 (10H, m, piperidine protons), 3.90 (2H, s, 8-CH_2), 3.92 (3H, s, 5-OCH_3), 6.31 (1H, s, H-6), 7.36 (2H, d, ^3J = 8.4, H-3′, H-5′), 7.48 (2H, d, ^3J = 8.4, H-2′, H-6′), 7.74 (1H, s, H-2), 10.55 (1H, s, 7-OH).

7-Hydroxy-5-methoxy-3-(2-methoxyphenyl)-8-(piperidin-1-ylmethyl)-4*H*-chromen-4-one (7e). $C_{23}H_{25}NO_5$, yield 78%, mp 167–168°C. PMR spectrum (400 MHz, $CDCl_3$, δ, ppm): 1.22–3.23 (10H, m, piperidine protons), 3.79 (3H, s, 2′-OCH_3), 3.90 (3H, s, 5-OCH_3), 3.91 (2H, s, 8-CH_2), 6.30 (1H, s, H-6), 6.91–7.02 (2H, m, H-3′, H-5′), 7.26–7.38 (2H, m, H-4′, H-6′), 7.71 (1H, s, H-2).

7-Hydroxy-8-[(4-methylpiperazin-1-yl)methyl]-5-methoxy-3-phenyl-4*H*-chromen-4-one (8a). $C_{22}H_{24}N_2O_4$, yield 60%, mp 189–190°C. PMR spectrum (400 MHz, $CDCl_3$, δ, ppm): 2.14–3.10 (11H, m, piperazine protons), 3.93 (3H, s, 5-OCH_3), 3.95 (2H, s, 8-CH_2), 6.33 (1H, s, H-6), 7.32–7.43 (3H, m, H-2′, H-4′, H-6′), 7.50–7.56 (2H, m, H-3′, H-5′), 7.71 (1H, s, H-2).

7-Hydroxy-8-[(4-methylpiperazin-1-yl)methyl]-5-methoxy-3-(4-chlorophenyl)-4*H*-chromen-4-one (8d). $C_{22}H_{23}ClN_2O_4$, yield 55%, mp 195–197°C. PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.04–3.22 (11H, m, piperazine protons), 3.93 (3H, s, 5-OCH_3), 3.95 (2H, s, 8-CH_2), 6.33 (1H, s, H-6), 7.36 (2H, d, ^3J = 8.5, H-3′, H-5′), 7.48 (2H, d, ^3J = 8.5, H-2′, H-6′), 7.76 (1H, s, H-2).

7-Hydroxy-8-[(4-methylpiperazin-1-yl)methyl]-5-methoxy-3-(2-methoxyphenyl)-4*H*-chromen-4-one (8e). $C_{23}H_{26}N_2O_5$, yield 83%, mp 164–166°C. PMR spectrum (400 MHz, $CDCl_3$, δ, ppm): 2.13–3.15 (11H, m, piperazine protons), 3.78 (3H, s, 2′-OCH_3), 3.90 (3H, s, 5-OCH_3), 3.95 (2H, s, 8-CH_2), 6.31 (1H, s, H-6), 6.92–7.03 (2H, m, H-3′, H-5′), 7.26–7.38 (2H, m, H-4′, H-6′), 7.74 (1H, s, H-2).

7-Hydroxy-5-methoxy-3-(4-methoxyphenyl)-8-(morpholin-4-ylmethyl)-4*H*-chromen-4-one (9b). $C_{22}H_{23}NO_6$, yield 73%, mp 199–200°C. PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.30–3.03 (4H, m, 3″-NCH_2, 5″-NCH_2), 3.74–3.87 [7H, m + s, $O(CH_2)_2$, 4′-OCH_3], 3.89 (3H, s, 5-OCH_3), 3.98 (2H, s, 8-CH_2), 6.36 (1H, s, H-6), 6.92 (2H, d, ^3J = 8.8, H-3′, H-5′), 7.46 (2H, d, ^3J = 8.8, H-2′, H-6′), 7.74 (1H, s, H-2).

7-Hydroxy-5-methoxy-8-(morpholin-4-ylmethyl)-3-(4-fluorophenyl)-4*H*-chromen-4-one (9c). $C_{21}H_{20}FNO_5$, yield 88%, mp 237–239°C. PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.38–3.08 (4H, m, 3″-NCH_2, 5″-NCH_2), 3.71–3.89 [4H, m, $O(CH_2)_2$], 3.92 (3H, s, 5-OCH_3), 3.98 (2H, s, 8-CH_2), 6.38 (1H, s, H-6), 7.09 (2H, dd, $^3J_{HH}$ = 8.8, $^3J_{HF}$ = 8.8, H-3′, H-5′), 7.50 (2H, dd, $^3J_{HH}$ = 8.8, $^4J_{HF}$ = 5.4, H-2′, H-6′), 7.76 (1H, s, H-2).

7-Hydroxy-5-methoxy-8-(morpholin-4-ylmethyl)-3-(4-chlorophenyl)-4*H*-chromen-4-one (9d). $C_{21}H_{20}ClNO_5$, yield 83%, mp 210–211°C. PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.38–3.23 (4H, m, 3″-NCH_2, 5″-NCH_2), 3.72–3.86 [4H, m, $O(CH_2)_2$], 3.89 (3H, s, 5-OCH_3), 4.00 (2H, s, 8-CH_2), 6.38 (1H, s, H-6), 7.35 (2H, d, ^3J = 8.5, H-3′, H-5′), 7.46 (2H, d, ^3J = 8.5, H-2′, H-6′), 7.76 (1H, s, H-2).

7-Hydroxy-5-methoxy-3-(2-methoxyphenyl)-8-(morpholin-4-ylmethyl)-4*H*-chromen-4-one (9e). $C_{22}H_{23}NO_6$, yield 83%, mp 179–180°C. PMR spectrum (400 MHz, $CDCl_3$, δ, ppm): 2.24–3.04 (4H, m, NCH_2-3″, NCH_2-5″), 3.67–3.88 [7H, m + s, $O(CH_2)_2$, 2′-OCH_3], 3.90 (3H, s, 5-OCH_3), 3.95 (2H, s, 8-CH_2), 6.32 (1H, s, H-6), 6.93–7.02 (2H, m, H-3′, H-5′), 7.25–7.38 (2H, m, H-2′, H-6′), 7.73 (1H, s, H-2).

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