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SYNTHESIS OF FORMONONETIN ANALOGS

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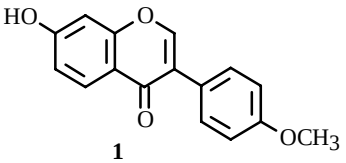
Derivatives of the natural isoflavone formononetin were synthesized. Acylation and alkylation of the phenolic hydroxyls and the chromone ring were investigated.

Key words: isoflavonoids, alkylation, aminomethylation, acylation.

The search for new highly effective bioregulators among modified analogs of natural isoflavones is very promising. They are used in medical practice [1] owing to the broad spectrum of physiological activity and low toxicity.

Isoflavonoids containing a methoxy in the para-position of ring B are used as natural antioxidants [2] and for prophylaxis of cardiovascular diseases [3] and breast [4] and prostate [5] cancers.

The natural isoflavonoid formononetin (7-hydroxy-4′-methoxyisoflavone) (**1**) possesses hypolipidemic activity [6] and lowers the cholesterol, triglyceride, phospholipid, and β-lipoprotein levels in blood [7, 8].



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In order to modify formononetin, we performed alkylation, acylation, and aminomethylation of isoflavones **2**-**5** [9-12].

Alkylation in acetone in the presence of freshly calcined potash produced 7-phenyloxy- and 7-phenylallyloxyisoflavones and ethyl 4-oxo-4*H*-chromenyl-7-hydroxyacetate (**6**-**8**).

Acylation of 7-hydroxyisoflavones proceeded readily in pyridine at room temperature. The acylating reagents were chlorides of naturally occurring acids (trimethylgallic, veratric, cinnamic, benzodioxolcarboxylic) and heterocyclic acids (substituted 3-benzofurancarboxylic, furan- and thiophenecarboxylic). Esters of methanesulfonic and carbonic acids of isoflavones were synthesized by reactions with methanesulfonylchloride and ethylchloroformate. Urethanes were prepared by acylation of N,N-disubstituted carbamoyl chlorides.

Mannich bases (**22**-**29**) were prepared by C-alkylation of the chromone ring. Aminomethyl derivatives of 7-hydroxyisoflavones were synthesized using various aminals based on piperidine or piperazine. Reaction of an equivalent amount of aminal in boiling dioxane led to aminomethylation of the chromone ring in the 8-position.

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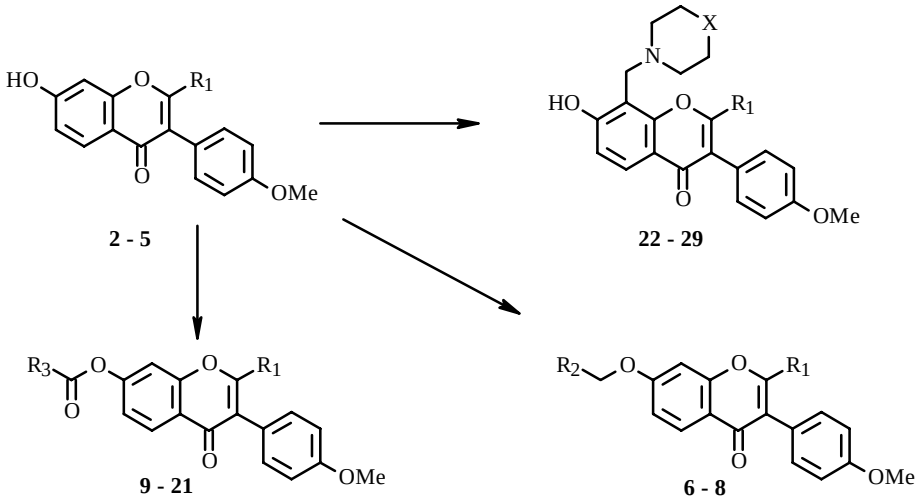

2: R_1 = H;
3: R_1 = Me;
4: R_1 = CF_3;
5: R_1 = COOEt;
6: R_1 = Me, R_2 = C_6H_5CH=CH;
7: R_1 = Me, R_2 = C_2H_5OCO;
8: R_1 = Me, R_2 = C_6H_6CO;
9: R_1 = Me, R_3 = 3,4,5-$(MeO)_5C_6H_2$;
10: R_1 = Me, R_3 = 3,4-$(MeO)_2C_6H_3$;
11: R_1 = CF_3, R_3 = C_6H_5-CH=CH;
12: R_1 = Me, R_3 = C_6H_5CH=CH;
13: R_1 = H, R_3 = C_2H_5O;
14: R_1 = Me, R_3 = C_2H_5O;
15: R_1 = COOEt, R_3 = furyl-2;
16: R_1 = Me, R_3 = thienyl-2;
17: R_1 = CF_3, R_3 = thienyl-2;
18: R_1 = H; R_3 = 3,4-methylenedioxyphenyl;
19: R_1 = Me, R_3 = 3,4-methylenedioxyphenyl;
20: R_1 = Me, R_3 = 2-phenyl-5-ethoxybenzofuryl-2;
21: R_1 = COOEt, R_3 = 2-methyl-5-acetoxybenzofuryl-2;
22: R_1 = Me, X = CH_2;
23: R_1 = CF_3, X = CH_2;
24: R_1 = H, X = $CHCH_3$;
25: R_1 = Me, X = $CHCH_3$;
26: R_1 = Me, X = N-CH_3;
27: R_1 = H, X = NCH_2CH_2OH;
28: R_1 = Me, X = NCH_2CH_2OH;
29: R_1 = CF_3, X = NCH_2CH_2OH

EXPERIMENTAL

The course of reactions and purity of products were monitored by TLC on Sorbfil UV-254 (Russia) and Merck (Germany) plates. The eluent was $CHCl_3$:CH_3OH (95:5 and 9:1). PMR spectra were measured on VXR-300 and Mercury 400 (Varian, 300 and 400 MHz, respectively) instruments in DMSO-d_6 (Mannich bases in $CDCl_3$) relative to TMS (internal standard) on the δ scale. Elemental analyses of all compounds corresponded with those calculated.

Starting compounds for the synthesis of formononetin derivatives were 7-hydroxyisoflavones **2-5** [9-12]: **7-hydroxy-3-(4-methoxyphenyl)chromen-4-one (2)**, **7-hydroxy-3-(4-methoxyphenyl)-2-methylchromen-4-one (3)**, **7-hydroxy-3-(4-methoxyphenyl)-2-trifluoromethylchromen-4-one (4)**, and **ethyl 7-hydroxy-3-(4-methoxyphenyl)-4-oxo-4*H*-chromen-2-carboxylate (5)**.

General Method for Preparing 7-Alkyloxyisoflavones (6-8). A hot solution of the appropriate 7-hydroxyisoflavone (10 mmol) in absolute acetone (30 mL) was treated with freshly calcined potash (2.1 g, 15 mmol), stirred, boiled, and treated with the corresponding alkylhalide (12 mmol). The reaction mixture was stored for 1-4 h (completion of the reaction determined by TLC) and poured into acidified icewater (100 mL). The resulting precipitate was filtered off and crystallized from a suitable solvent.

3-(4-Methoxyphenyl)-2-methyl-7-(3-phenylallyloxy)-chromen-4-one (6), mp 152-153°C (propan-2-ol). PMR* (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.26 (3H, s, Me-2), 3.79 (3H, s, OMe-4′), 6.98 (2H, d, ^{3}J = 8.8, H-3′, H-5′), 7.20 (2H, d, ^{3}J = 8.8, H-2′, H-6′), 7.10 (1H, dd, ^{3}J = 8.8, ^{4}J = 2.4, H-6), 7.19 (1H, d, ^{4}J = 2.4, H-8), 7.95 (1H, d, ^{3}J = 8.8, H-5), alkyl protons: 4.89 (2H, d, ^{3}J = 5.6, OCH_2-7), 6.55 (1H, m, ^{3}J = 5.6, ^{3}J = 16.0, CH=CH), 6.82 (1H, d, ^{3}J = 16.0, CH=CH), 7.28-7.51 (5H, m, phenyl protons).

3-(4-Methoxyphenyl)-2-methyl-7-(2-oxo-2-phenylethoxy)-chromen-4-one (7), mp 178-179°C (methanol). PMR (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.24 (3H, s, Me-2), 3.79 (3H, s, OMe-4′), 6.98 (2H, d, ^{3}J = 8.8, H-3′, H-5′), 7.20 (2H, d, ^{3}J = 8.8, H-2′, H-6′), 7.12 (1H, dd, ^{3}J = 8.8, ^{4}J = 2.4, H-6), 7.23 (1H, d, ^{4}J = 2.4, H-8), 7.94 (1H, d, ^{3}J = 8.8, H-5), alkyl protons: 5.81 (2H, s, OCH_2-7), 7.72-8.06 (5H, m, phenyl protons).

Ethyl [3-(4-methoxyphenyl)-2-methyl-4-oxo-4*H*-chromen-7-yloxy]-acetate (8), mp 108.5-109.5°C (methanol). PMR (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.27 (3H, s, Me-2), 3.81 (3H, s, OMe-4′), 6.99 (2H, d, ^{3}J = 8.8, H-3′, H-5′), 7.21 (2H, d, ^{3}J = 8.8, H-2′, H-6′), 7.09 (1H, dd, ^{3}J = 8.8, ^{4}J = 2.4, H-6), 7.15 (1H, d, ^{4}J = 2.4, H-8), 7.96 (1H, d, ^{3}J = 8.8, H-5), alkyl protons: 4.99 (2H, s, OCH_2-7), 4.21 (2H, q, OCH_2, ^{3}J = 6.8), 1.24 (3H, t, CH_3, ^{3}J = 6.8).

General Method for Preparing 7-Acyloxyisoflavones (9-21). A solution of the appropriate 7-hydroxyisoflavone (10 mmol) in the minimum amount of absolute pyridine was treated with the acid chloride (12 mmol). The reaction mixture was stored for 1 d at room temperature and the poured into icewater. The resulting precipitate was filtered off and crystallized from a suitable solvent.

3-(4-Methoxyphenyl)-2-methyl-4-oxo-4*H*-chromen-7-yl 3,4,5-trimethoxybenzoate (9), mp 218-219°C (propan-2-ol:DMF). PMR (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.30 (3H, s, Me-2), 3.79 (3H, s, OMe-4′), 7.00 (2H, d, ^{3}J = 8.8, H-3′, H-5′), 7.23 (2H, d, ^{3}J = 8.8, H-2′, H-6′), 7.42 (1H, dd, ^{3}J = 8.0, ^{4}J = 1.6, H-6), 7.67 (1H, d, ^{4}J = 1.6, H-8), 8.96 (1H, d, ^{3}J = 8.0, H-5), acyl protons: 7.44 (2H, s, H-2, H-6), 3.80-3.88 (3H, s, each 3×OCH_3-3,4,5).

3-(4-Methoxyphenyl)-2-methyl-4-oxo-4*H*-chromen-7-yl 3,4-dimethoxybenzoate (10), mp 197-198°C (propan-2-ol). PMR (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.30 (3H, s, Me-2), 3.80 (3H, s, OMe-4′), 7.01 (2H, d, ^{3}J = 8.8, H-3′, H-5′), 7.24 (2H, d, ^{3}J = 8.8, H-2′, H-6′), 7.41 (1H, dd, ^{3}J = 8.0, ^{4}J = 2.0, H-6), 7.66 (1H, d, ^{4}J = 2.0, H-8), 8.11 (1H, d, ^{3}J = 8.0, H-5), acyl protons: 7.61 (1H, d, ^{4}J = 1.6, H-2), 7.17 (1H, d, ^{3}J = 8.8, H-5), 7.82 (1H, dd, ^{3}J = 8.8, ^{4}J = 1.6, H-6), 3.86-3.89 (3H, s, each 2×OCH_3-3,4).

3-(4-Methoxyphenyl)-4-oxo-2-trifluoromethyl-4*H*-chromen-7-yl 3-phenylacrylate (11), mp 159-160°C (propan-2-ol). PMR (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 3.82 (3H, s, OMe-4′), 7.03 (2H, d, ^{3}J = 8.8, H-3′, H-5′), 7.24 (2H, d, ^{3}J = 8.8, H-2′, H-6′), 7.48 (1H, dd, ^{3}J = 8.8, ^{4}J = 2.4, H-6), 7.81 (1H, d, ^{4}J = 2.4, H-8), 8.16 (1H, d, ^{3}J = 8.8, H-5), acyl protons: 6.96 (1H, d, ^{3}J = 16.0, $C_6H_5CH=\underline{CH}$), 7.96 (1H, d, ^{3}J = 16.0, $C_6H_5\underline{CH}=CH$), 7.48-7.53 (5H, m, phenyl protons).

3-(4-Methoxyphenyl)-2-methyl-4-oxo-4*H*-chromen-7-yl 3-phenylacrylate (12), mp 182-183°C (propan-2-ol). PMR (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.27 (3H, s, Me-2), 3.81 (3H, s, OMe-4′), 7.01 (2H, d, ^{3}J = 8.8, H-3′, H-5′), 7.24 (2H, d, ^{3}J = 8.8, H-2′, H-6′), 7.36 (1H, dd, ^{3}J = 8.0, ^{4}J = 2.4, H-6), 7.61 (1H, d, ^{4}J = 2.4, H-8), 8.11 (1H, d, ^{3}J = 8.0, H-5), acyl protons: 6.95 (1H, d, ^{3}J = 16.0, $C_6H_5CH=\underline{CH}$), 7.95 (1H, d, ^{3}J = 16.0, $C_6H_5\underline{CH}=CH$), 7.48-7.89 (5H, m, phenyl protons).

Ethyl 3-(4-methoxyphenyl)-4-oxo-4*H*-chromen-7-ylcarboxylate (13), mp 135-136°C (methanol). PMR (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 8.52 (1H, s, H-2), 3.79 (3H, s, OMe-4′), 7.01 (2H, d, ^{3}J = 9.0, H-3′, H-5′), 7.54 (2H, d, ^{3}J = 9.0, H-2′, H-6′), 7.42 (1H, dd, ^{3}J = 9.0, ^{4}J = 1.8, H-6), 7.70 (1H, d, ^{4}J = 1.8, H-8), 8.18 (1H, d, ^{3}J = 9.0, H-5), acyl protons: 4.31 (2H, q, ^{3}J = 6.9, OCH_2), 1.32 (3H, t, ^{3}J = 6.9, CH_3).

Ethyl 3-(4-methoxyphenyl)-2-methyl-4-oxo-4*H*-chromen-7-ylcarboxylate (14), mp 122-123°C (methanol). PMR (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.29 (3H, s, Me-2), 3.80 (3H, s, OMe-4′), 7.00 (2H, d, ^{3}J = 8.7, H-3′, H-5′), 7.22 (2H, d, ^{3}J = 8.7, H-2′, H-6′), 7.37 (1H, dd, ^{3}J = 8.7, ^{4}J = 2.1, H-6), 7.63 (1H, d, ^{4}J = 2.1, H-8), 8.08 (1H, d, ^{3}J = 8.7, H-5), acyl protons: 4.31 (2H, q, ^{3}J = 7.2, OCH_2), 1.32 (3H, t, ^{3}J = 7.2, CH_3).

Ethyl 7-(furan-2-carbonyloxy)-3-(4-methoxyphenyl)-4-oxo-4*H*-chromen-2-carboxylate (15), mp 131.5-132.5°C (propan-2-ol). PMR (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 0.98, 4.13 (3H, t; 2H, q, ^{3}J = 7.2, CH_3CH_2OOC-2), 3.80 (3H, s, OMe-4′), 6.99 (2H, d, ^{3}J = 8.8, H-3′, H-5′), 7.20 (2H, d, ^{3}J = 8.8, H-2′, H-6′), 7.50 (1H, dd, ^{3}J = 8.8, ^{4}J = 2.4, H-6), 7.80 (1H, d, ^{4}J = 2.4, H-8), 8.17 (1H, d, ^{3}J = 8.8, H-5), acyl protons: 7.66, 8.52, 8.16 (3H, m, H-2,3,4).

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*Primed chemical shifts refer to the 3-phenyl substituent.

3-(4-Methoxyphenyl)-2-methyl-4-oxo-4*H*-chromen-7-yl thiophen-2-carboxylate (16), mp 171-172°C (propan-2-ol). PMR (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.30 (3H, s, Me-2), 3.81 (3H, s, OMe-4′), 7.01 (2H, d, ^{3}J = 8.8, H-3′, H-5′), 7.24 (2H, d, ^{3}J = 8.8, H-2′, H-6′), 7.42 (1H, dd, ^{3}J = 8.8, ^{4}J = 2.0, H-6), 7.70 (1H, d, ^{4}J = 2.0, H-8), 8.12 (1H, d, ^{3}J = 8.8, H-5), acyl protons: 8.15, 7.35, 8.09 (3H, m, H-2,3,4).

3-(4-Methoxyphenyl)-4-oxo-2-trifluoromethyl-4*H*-chromen-7-yl thiophen-2-carboxylate (17), mp 153-154°C (propan-2-ol). PMR (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.51 (3H, s, Me-2), 3.82 (3H, s, OMe-4′), 7.03 (2H, d, ^{3}J = 8.7, H-3′, H-5′), 7.25 (2H, d, ^{3}J = 8.7, H-2′, H-6′), 7.54 (1H, dd, ^{3}J = 8.8, ^{4}J = 2.4, H-6), 7.90 (1H, d, ^{4}J = 2.4, H-8), 8.12 (1H, d, ^{3}J = 8.8, H-5), acyl protons: 8.17, 7.36, 8.19 (3H, m, H-2,3,4).

3-(4-Methoxyphenyl)-4-oxo-4*H*-chromen-7-yl benzo[1,3]dioxol-5-carboxylate (18), mp 265-266°C (DMF). PMR (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 8.50 (1H, s, H-2), 3.79 (3H, s, OMe-4′), 7.01 (2H, d, ^{3}J = 8.8, H-3′, H-5′), 7.55 (2H, d, ^{3}J = 8.80, H-2′, H-6′), 7.44 (1H, dd, ^{3}J = 8.8, ^{4}J = 2.00, H-6), 7.59 (1H, d, ^{4}J = 2.00, H-8), 8.20 (1H, d, ^{3}J = 8.8, H-5), 8.50 (1H, s, H-2), acyl protons: 7.72 (1H, d, ^{4}J = 1.6, H-2), 7.13 (1H, d, ^{3}J = 8.8, H-5), 7.79 (1H, dd, ^{3}J = 8.8, ^{4}J = 1.6, H-6), 6.20 (2H, s, each 2×OCH_2O).

3-(4-Methoxyphenyl)-2-methyl-4-oxo-4*H*-chromen-7-yl benzo[1,3]dioxol-5-carboxylate (19), mp 196-197°C (DMF). PMR (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.29 (3H, s, Me-2), 3.79 (3H, s, OMe-4′), 6.99 (2H, d, ^{3}J = 8.8, H-3′, H-5′), 7.23 (2H, d, ^{3}J = 8.8, H-2′, H-6′), 8.40 (1H, dd, ^{3}J = 8.4, ^{4}J = 2.4, H-6), 7.65 (1H, d, ^{4}J = 2.4, H-8), 8.10 (1H, d, ^{3}J = 8.4, H-5), acyl protons: 7.59 (1H, d, ^{4}J = 1.6, H-2), 7.14 (1H, d, ^{3}J = 8.0, H-5), 7.89 (1H, dd, ^{3}J = 8.0, ^{4}J = 1.6, H-6), 6.20 (2H, s, each 2×OCH_2O).

3-(4-Methoxyphenyl)-2-methyl-4-oxo-4*H*-chromen-7-yl 5-ethoxy-2-phenylbenzofuran-3-carboxylate (20), mp 127-128°C (DMF). PMR (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.30 (3H, s, Me-2), 3.81 (3H, s, OMe-4′), 7.01 (2H, d, ^{3}J = 8.8, H-3′, H-5′), 7.24 (2H, d, ^{3}J = 8.8, H-2′, H-6′), 7.09 (1H, dd, ^{3}J = 8.4, ^{4}J = 2.4, H-6), 7.54 (1H, d, ^{4}J = 2.4, H-8), 8.12 (1H, d, ^{3}J = 8.4, H-5), acyl protons: 7.45 (1H, dd, ^{3}J = 8.8, ^{4}J = 2.0, H-6), 7.75 (1H, d, ^{4}J = 2.0, H-4), 7.71 (1H, d, ^{3}J = 8.4, H-7), 7.61-7.52, 8.10-8.03 (5H, m, phenyl protons), 4.11 (2H, q, OCH_2-5, ^{3}J = 6.4), 1.37 (3H, t, CH_3, ^{3}J = 6.4).

Ethyl 7-(5-acetoxy-2-methylbenzofuran-3-carbonyloxy)-3-(4-methoxyphenyl)-4-oxo-4*H*-chromen-2-carboxylate (21), mp 126-127°C (DMF). PMR (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.00, 4.15 (3H, t, 2H, q, ^{3}J = 7.2, CH_3CH_2OOC-2), 3.82 (3H, s, OMe-4′), 7.01 (2H, d, ^{3}J = 8.8, H-3′, H-5′), 7.24 (2H, d, ^{3}J = 8.8, H-2′, H-6′), 7.19 (1H, dd, ^{3}J = 8.4, ^{4}J = 2.4, H-6), 7.69 (1H, d, ^{4}J = 2.4, H-8), 8.20 (1H, d, ^{3}J = 8.8, H-5), acyl protons: 2.87 (3H, s, CH_3-2), 2.30 (3H, s, $OCOCH_3$-5), 7.58 (1H, dd, ^{3}J = 8.8, ^{4}J = 2.0, H-6), 7.88 (1H, d, ^{4}J = 2.0, H-4), 7.75 (1H, d, ^{3}J = 8.8, H-7).

General Method for Preparing 8-Dialkylaminomethylisoflavones (22-29). A boiling solution of the appropiate isoflavone (10 mmol) in absolute dioxane (20 mL) was treated with the corresponding aminal (15 mmol). The reaction mixture was refluxed for 1h (completion of the reaction monitored by TLC), cooled, and evporated in vacuo. The solid was crystallized from a suitable solvent.

7-Hydroxy-3-(4-methoxyphenyl)-2-methyl-8-piperidin-1-ylmethylchromen-4-one (22), mp 195-196°C (propan-2-ol). PMR (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.23-3.34 (10H, m, piperidine protons), 2.28 (3H, s, Me-2), 3.98 (2H, s, NCH_2), 3.83 (3H, s, OMe-4′), 6.95 (2H, d, ^{3}J = 8.0, H-3′, H-5′), 7.19 (2H, d, ^{3}J = 8.0, H-2′, H-6′), 6.82 (1H, d, ^{3}J = 8.0, H-6), 8.03 (1H, d, ^{3}J = 8.0, H-5), 7.5-8.0 (1H, s, 7-OH).

7-Hydroxy-3-(4-methoxyphenyl)-8-piperidin-1-ylmethyl-2-trifluoromethylchromen-4-one (23), mp 161-162°C (propan-2-ol). PMR (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.27-3.30 (10H, m, piperidine protons), 4.00 (2H, s, NCH_2), 3.84 (3H, s, OMe-4′), 6.96 (2H, d, ^{3}J = 9.0, H-3′, H-5′), 7.18 (2H, d, ^{3}J = 9.0, H-2′, H-6′), 6.89 (1H, d, ^{3}J = 9.0, H-6), 8.02 (1H, d, ^{3}J = 9.0, H-5), 11.4 (1H, s, 7-OH).

7-Hydroxy-3-(4-methoxyphenyl)-8-(4-methylpiperidin-1-ylmethyl)-chromen-4-one (24), mp 191.5-192.5°C (propan-2-ol:hexane). PMR (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.27-3.35 (13H, m, piperidine protons), 3.99 (2H, s, NCH_2), 3.84 (3H, s, OMe-4′), 7.01 (2H, d, ^{3}J = 9.0, H-3′, H-5′), 7.54 (2H, d, ^{3}J = 9.0, H-2′, H-6′), 6.86 (1H, d, ^{3}J = 9.0, H-6), 8.01 (1H, d, ^{3}J = 9.0, H-5), 7.86 (1H, s, H-2), 10.51 (1H, s, 7-OH).

7-Hydroxy-3-(4-methoxyphenyl)-2-methyl-8-(4-methylpiperidin-1-ylmethyl)-chromen-4-one (25), mp 178-179°C (propan-2-ol:hexane). PMR (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.20-3.11 (13H, m, piperidine protons), 2.28 (3H, s, Me-2), 3.99 (2H, s, NCH_2), 3.83 (3H, s, OMe-4′), 6.95 (2H, d, ^{3}J = 8.4, H-3′, H-5′), 7.19 (2H, d, ^{3}J = 8.4, H-2′, H-6′), 6.82 (1H, d, ^{3}J = 9.0, H-6), 8.02 (1H, d, ^{3}J = 9.0, H-5), 9.0-10.0 (1H, s, 7-OH).

7-Hydroxy-3-(4-methoxyphenyl)-2-methyl-8-(4-methylpiperazin-1-ylmethyl)-chromen-4-one (26), mp 181-182°C (propan-2-ol). PMR (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.00-3.25 (8H, m, piperazine protons), 2.33 (3H, s, NCH_3), 2.30 (3H, s, Me-2), 4.02 (2H, s, NCH_2), 3.83 (3H, s, OMe-4′), 6.95 (2H, d, ^3J = 8.4, H-3′, H-5′), 7.19 (2H, d, ^3J = 8.4, H-2′, H-6′), 6.83 (1H, d, ^3J = 8.8, H-6), 8.04 (1H, d, ^3J = 8.8, H-5), 10.0-12.0 (1H, s, 7-OH).

7-Hydroxy-8-[4-(2-hydroxyethyl)-piperazin-1-ylmethyl]-3-(4-methoxyphenyl)-chromen-4-one (27), mp 165-166°C (propan-2-ol). PMR (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.22-3.00 (8H, m, piperazine protons), 2.60 (2H, t, NCH_2, ^3J = 5.4), 3.64 (2H, t, CH_2O, ^3J = 5.4), 4.04 (2H, s, NCH_2), 3.83 (3H, s, OMe-4′), 6.96 (2H, d, ^3J = 9.0, H-3′, H-5′), 7.49 (2H, d, ^3J = 9.0, H-2′, H-6′), 8.12 (1H, d, ^3J = 9.0, H-6), 6.88 (1H, d, ^3J = 9.0, H-5), 7.89 (1H, s, H-2), 10.0-12.0 (1H, s, 7-OH).

7-Hydroxy-8-[4-(2-hydroxyethyl)-piperazin-1-ylmethyl]-3-(4-methoxyphenyl)-2-methylchromen-4-one (28), mp 205-206°C (propan-2-ol). PMR (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.40-3.00 (8H, m, piperazine protons), 2.60 (2H, t, NCH_2, ^3J = 5.4), 3.64 (2H, t, CH_2O, ^3J = 5.4), 2.30 (3H, s, Me-2), 4.04 (2H, s, NCH_2), 3.84 (3H, s, OMe-4′), 6.96 (2H, d, ^3J = 8.7, H-3′, H-5′), 7.20 (2H, d, ^3J = 8.7, H-2′, H-6′), 6.83 (1H, d, ^3J = 8.4, H-6), 8.04 (1H, d, ^3J = 8.4, H-5), 10.0-12.0 (1H, s, 7-OH).

7-Hydroxy-8-[4-(2-hydroxyethyl)-piperazin-1-ylmethyl]-3-(4-methoxyphenyl)-2-trifluoromethylchromen-4-one (29), mp 184-185°C (propan-2-ol). PMR (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.29-3.00 (8H, m, piperazine protons), 2.60 (2H, t, NCH_2, ^3J = 5.4), 3.64 (2H, t, CH_2O, ^3J = 5.4), 4.06 (2H, s, NCH_2), 3.84 (3H, s, OMe-4′), 6.96 (2H, d, ^3J = 9.0, H-3′, H-5′), 7.18 (2H, d, ^3J = 9.0, H-2′, H-6′), 6.92 (1H, d, ^3J = 9.0, H-6), 8.05 (1H, d, ^3J = 9.0, H-5), 10.0-12.0 (1H, s, 7-OH).

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