SYNTHESIS OF 4-AMINOMETHYL ANALOGS OF DAPHNETIN

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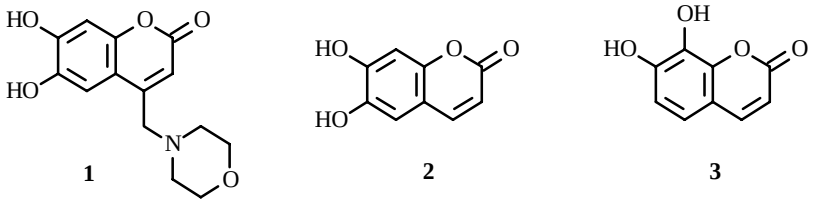
4-Aminomethyl analogs of the natural coumarin daphnetin were synthesized. The reaction of 4-chloromethylcoumarins with aliphatic and aromatic amines was studied.

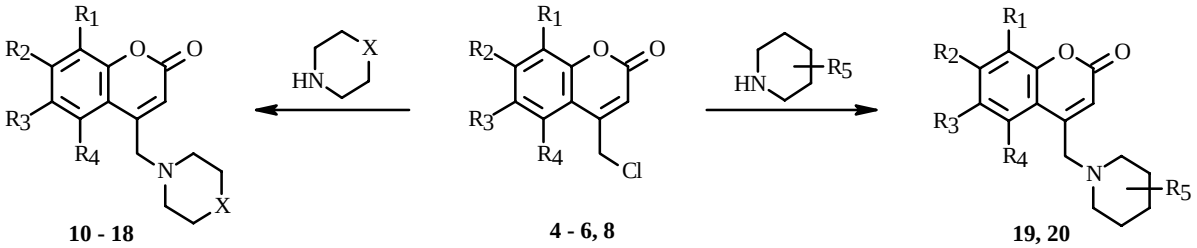
Key words: esculetin, daphnetin, coumarin, alkylation.

Coumarin derivatives are widely used in medical practice as pharmacological preparations with a broad spectrum of biological activity [1-3]. Effective methods of developing new bioactive coumarins include chemical modification of natural coumarins [4] and introduction of new pharmacophores into the coumarin core [5, 6]. It is known that the presence of a group containing a basic tertiary N atom or amine significantly improves the bioavailability of the compounds [7]. A good example of this is the capillary protectant folescutol (**1**), a derivative of the natural coumarin esculetin (**2**).



1 **2** **3**

Therefore, it seemed of practical interest to develop synthetic methods for 4-aminomethylcoumarins containing not only a basic tertiary N atom but also a free N–H group and to prepare aminomethyl derivatives of the natural coumarin daphnetin (**3**). For this we proposed alkylation of primary and secondary amines by substituted 4-chloromethylcoumarins.



10 - 18 **4 - 6, 8** **19, 20**

4, 10: R_2 = OMe, X = O, $R_1 = R_3 = R_4$ = H; **5, 11:** R_2 = Me, X = NH, $R_1 = R_3 = R_4$ = H
6, 12: $R_1 = R_2$ = Me, X = N-Ph-4-OMe, $R_3 = R_4$ = H; **8, 13:** $R_1 = R_2$ = OH, X = O, $R_3 = R_4$ = H
5, 14: R_2 = Me, X = -CH_2CH_2-, $R_1 = R_3 = R_4$ = H; **6, 15:** $R_1 = R_2$ = Me, X = N-COOEt, $R_3 = R_4$ = H
5, 16: R_2 = Me, X = N-CH_2Ph, $R_1 = R_3 = R_4$ = H; **5, 17:** R_2 = Me, X = N-CH_2-Ph-3′,4′-OCH_2O, $R_1 = R_3 = R_4$ = H
8, 18: $R_1 = R_2$ = OH, X = O, 2′,6′-Me , $R_3 = R_4$ = H; **5, 19:** R_2 = Me, R_5 = 2′-CH_2CH_2OH, $R_1 = R_3 = R_4$ = H
6, 20: $R_1 = R_2$ = Me, R_5 = 4′,4′-OCH_2CH_2O, $R_3 = R_4$ = H

Starting 4-chloromethylcoumarins were prepared by Pechmann condensation of substituted phenols with 4-chloroacetoacetic esters in the presence of conc. H_2SO_4 [8-11]. Secondary aliphatic amines reacted smoothly with 4-chloromethylcoumarins in high yields (75-90%) in DMF without heating.

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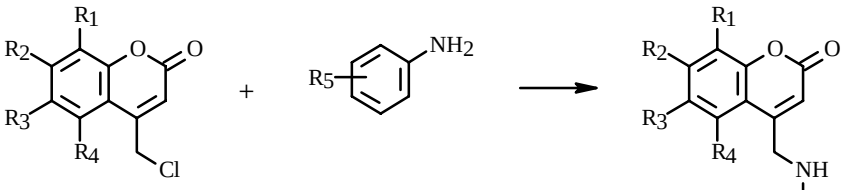

5 - 7, 9

21 - 28

6, 21: $R_1 = R_2 = Me$, $R_5 = 4\text{-}OEt$, $R_3 = R_4 = H$; **5, 22:** $R_2 = Me$, $R_5 = 2,5\text{-}COOMe_2$, $R_1 = R_3 = R_4 = H$
7, 23: $R_3 = OH$, $R_2 = Me$, $R_5 = 2\text{-}F$, $R_1 = R_4 = H$; **9, 24:** $R_3 = OH$, $R_2 = Ph$, $R_5 = 3\text{-}Cl$, $R_1 = R_4 = H$
7, 25: $R_3 = OH$, $R_2 = Me$, $R_5 = 3\text{-}OMe$, $R_1 = R_4 = H$; **7, 26:** $R_3 = OH$, $R_2 = Me$, $R_5 = 4\text{-}OEt$, $R_1 = R_4 = H$
9, 27: $R_3 = OH$, $R_2 = Ph$, $R_5 = 2\text{-}COOMe$, $R_1 = R_4 = H$; **7, 28:** $R_3 = OH$, $R_2 = Me$, $R_5 = 2,3\text{-}Me_2$, $R_1 = R_4 = H$

The presence of free hydroxyls in both 4-chloromethylcoumarins **13** and **18** and amine **19** did not hinder the alkylation at the N atom. On the other hand, use of a six-fold excess of piperazine enabled monoalkylated **11** with a free secondary amino group to be produced.

The substituted 4-chloromethylcoumarins turned out to be rather reactive toward alkylation of primary aromatic amines. The duration of the reaction and the yield depended directly on the nucleophilicity of the amine. The reaction was carried out in DMF with prolonged (48 h) heating.

The prepared 4-aminomethyl coumarin derivatives (**10**-**20**) were colorless crystalline compounds with low melting points and were readily soluble in organic solvents. Conversely, **21-28** were high melting and difficultly soluble. The PMR spectra of **21**-**28** exhibited a triplet for the secondary amine at 5.5-6.5 ppm. The methylene bound to the amine appeared as a doublet at 4.4-4.7 ppm.

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). Melting points were determined on a Kofler block. IR spectra were measured on a Nicolet FTIR Nexus 475 spectrometer; PMR spectra, on Varian VXR-300 and Mercury 400 (300 and 400 MHz, respectively) spectrometers in DMSO-d_6 relative to TMS (internal standard) on the δ-scale. Elemental analyses of all compounds agreed with those calculated.

Sarting 4-chloromethylcoumarins (**4**-**9**) were prepared as before [8-11].

General Method for Preparing 10-20. A hot solution of the appropriate 4-chloromethylcoumarin (10 mmol) in DMF (25 mL) was treated with seconary amine (22 mmol) and held for 24 h at room temperature (completion of reaction determined by TLC). The mixture was poured into cold water (200 mL). The precipitate was filtered off and crystallized from aqueous alcohol.

7-Methoxy-4-morpholin-4-ylmethylchromen-2-one (10). Yield 78%, $C_{15}H_{17}NO_4$, mp 152-153°C. IR spectrum (KBr, cm^{-1}): 1719, 1607, 1511, 1459, 1395, 1296, 1239, 1136. PMR spectrum: 2.49 (4H, br.s, H-2′,6′), 3.07 (4H, br.s, H-3′,5′), 3.65 (2H, s, CH_2-4), 3.85 (3H, s, OMe-7), 6.32 (3H, s, H-3), 6.98 (2H, m, H-6,8), 7.84 (1H, d, J = 8.4, H-5).

7-Methyl-4-piperazin-1-ylmethylchromen-2-one (11). Yield 70%, $C_{15}H_{18}N_2O_2$, mp 133-134°C. IR spectrum (KBr, cm^{-1}): 3380, 1726, 1676, 1594, 1487, 1355, 1286, 1242. PMR spectrum: 2.39 (m, 9H, piperazine protons), 3.66 (2H, s, CH_2-4), 6.41 (3H, s, H-3), 7.21 (2H, m, H-6,8), 7.79 (1H, d, J = 8.2, H-5).

4-[4-(4-Methoxyphenyl)-piperazin-1-ylmethyl]-7,8-dimethylchromen-2-one (12). Yield 86%, $C_{23}H_{26}N_2O_3$, mp 181-182°C. IR spectrum (KBr, cm^{-1}): 1716, 1700, 1626, 1588, 1494, 1392, 1362, 1292, 1232, 1129. PMR spectrum: 2.32 (3H, s, Me-6), 2.37 (3H, s, Me-8), 2.65 (4H, br.s, CH_2-3′,5′), 3.59 (5H, br.s, –OMe, CH_2-4), 6.39 (3H, s, H-3), 6.39 (2H, d, J = 8.4, Ph-2,6-H), 6.81 (2H, d, J = 8.4, Ph-3,5-H), 7.09 (1H, d, J = 8.4, H-6), 7.61 (1H, d, J = 8.4, H-5).

7,8-Dihydroxy-4-morpholin-4-ylmethylchromen-2-one (13). Yield 80%, $C_{14}H_{15}NO_5$, mp 146-147°C. IR spectrum (KBr, cm^{-1}): 3264, 1726, 1698, 1624, 1505, 1442, 1375, 1286, 1102. PMR spectrum: 3.58 (4H, br.s, CH_2-3′,5′), 3.60 (2H, s, CH_2-4), 6.25 (3H, s, H-3), 6.81 (1H, d, J = 8.5, H-6), 7.23 (1H, d, J = 8.5, H-5), 9.67 (2H, br.s, OH-7,8).

4-Azepan-1-ylmethyl-7-methylchromen-2-one (14). Yield 72%, $C_{17}H_{21}NO_2$, mp 121-122°C. IR spectrum (KBr, cm^{-1}): 1729, 1634, 1586, 1502, 1454, 1324, 1246, 1124, 1056. PMR spectrum: 2.46 (4H, br.s, CH_2-3′,5′), 3.60 (2H, s, CH_2-4), 6.25 (3H, s, H-3), 6.81 (1H, d, J = 8.4, H-5), 7.84 (1H, d, J = 8.4, H-6), 9.67 (2H, br.s, OH-7,8).

4-(7,8-Dimethyl-2-oxo-2*H*-chromen-4-ylmethyl)piperazin-1-carboxylic Acid Ethyl Ester (15). Yield 77%, $C_{19}H_{24}N_2O_4$, mp 161-162°C. IR spectrum (KBr, cm^{-1}): 1715, 1676, 1654, 1598, 1524, 1468, 1412, 1363, 1265, 1056. PMR spectrum: 1.18 (3H, t, J = 8.2, CH_2-4′), 4.02 (2H, q, J = 8.2, CH_3-4′), 2.27 (3H, s, Me-7), 2.35 (3H, s, Me-8), 3.69 (2H, s, CH_2-4), 2.45 (8H, br.s, piperazine protons), 6.42 (3H, s, H-3), 7.16 (1H, d, J = 8.4, H-6), 7.63 (1H, d, J = 8.4, H-5).

4-(4-Benzylpiperazin-1-ylmethyl)-7-methylchromen-2-one (16). Yield 75%, $C_{22}H_{24}N_2O_2$, mp 187-188°C. IR spectrum (KBr, cm^{-1}): 1729, 1676, 1596, 1480, 1376, 1278, 1215, 1168, 1096, 1044. PMR spectrum: 2.40 (11H, br.s, Me-7, piperazine protons), 3.46 (2H, s, CH_2-4′), 3.66 (2H, s, CH_2-4), 6.38 (3H, s H-3), 7.29 (7-H-Ph, m, H-7,8), 7.78 (1H, d, J = 8.4, H-5).

4-(4-Benzo[1,3]dioxol-5-ylmethylpiperazin-1-ylmethyl)-7-methylchromen-2-one (17). Yield 82%, $C_{23}H_{24}N_2O_4$, mp 161-162°C. IR spectrum (KBr, cm^{-1}): 1715, 1624, 1575, 1515, 1498, 1392, 1305, 1276, 1210, 1148, 1115. PMR spectrum: 2.40 (8H, br.s, piperazine protons), 3.36 (2H, s, CH_2-4′), 3.65 (2H, s, CH_2-4), 5.98 (2H, s, OCH_2O), 6.38 (3H, s, H-3), 6.74 (1H, d, J = 8.3, H-2′), 6.84 (2H, m, H-5′,6′), 7.19 (1H, dd, J = 8.4, 2.3, H-6), 7.21 (1H, d, J = 2.3, H-8), 7.78 (1H, d, J = 8.4, H-5).

4-(2,6-Dimethylmorpholin-4-ylmethyl)-7,8-dihydroxychromen-2-one (18). Yield 88%, $C_{16}H_{19}NO_5$, mp 136-137°C. IR spectrum (KBr, cm^{-1}): 3384, 1715, 1668, 1602, 1564, 1486, 1393, 1356, 1324, 1254, 1156, 1032. PMR spectrum: 1.03, 1.15, 1.76, 2.27, 2.35, 2.75, 3.62, 3.92 (14H, 9m, morpholine protons), 6.41 (3H, s, H-3), 7.15 (1H, d, J = 8.4, H-6), 7.67 (1H, d, J = 8.4, H-5).

4-[2-(2-Hydroxyethyl)piperidin-1-ylmethyl]-7-methylchromen-2-one (19). Yield 68%, $C_{18}H_{23}NO_3$, mp 132-133°C. IR spectrum (KBr, cm^{-1}): 3420, 1720, 1640, 1594, 1508, 1474, 1432, 1365, 1245 1185, 1130. PMR spectrum: 1.60, 2.63, 2.68, 3.42 (13H, 6m, piperidine protons), 2.32 (3H, s, Me-7), 6.46 (3H, s, H-3), 7.16 (1H, dd, J = 8.4, 2.3, H-6), 7.22 (1H, d, J = 2.3, H-8), 7.80 (1H, d, J = 8.4, H-5).

4-(1,4-Dioxa-8-azaspiro[4.5]dec-8-ylmethyl)-7,8-dimethylchromen-2-one (20). Yield 70%, $C_{19}H_{23}NO_4$, mp 155-156°C. IR spectrum (KBr, cm^{-1}): 1722, 1632, 1565, 1496, 1424, 1398, 1342, 1228, 1130. PMR spectrum: 1.63 (4H, br.s, H-3′,5′), 2.27 (3H, s, Me-7), 2.35 (3H, s, Me-8), 3.68 (2H, s, CH_2-4), 3.86 (4H, s, OCH_2CH_2O), 6.41 (3H, s, H-3), 7.16 (3H, s, H-6), 7.64 (3H, 5s, H-5).

General Method for Preparing 21-28. A hot solution of the appropriate 4-chloromethylcoumarin (10 mmol) in DMF (25 mL) was treated with amine (22 mmol) and held for 20-48 h at 80-100°C (completion of reaction determined by TLC). The mixture was cooled and poured into cold water (200 mL). The precipitate was filtered off and crystallized from isopropanol:DMF.

4-[(4-Ethoxyphenylamino)methyl]-7,8-dimethylchromen-2-one (21). Yield 70%, $C_{20}H_{21}NO_3$, mp 205-207°C. IR spectrum (KBr, cm^{-1}): 3260, 1726, 1696, 1624, 1576, 1513, 1482, 1415, 1242, 1208, 1174. PMR spectrum: 1.24 (3H, t, J = 8.2, CH_3-4′), 3.85 (2H, q, J = 8.2, CH_2-4′), 2.27 (3H, s, Me-7), 2.36 (3H, s, Me-8), 4.44 (2H, d, J = 6.5, CH_2-4), 5.92 (1H, t, J = 6.5, NH), 6.26 (3H, s, H-3), 6.54 (2H, d, J = 8.4, H-2′,6′), 6.68 (2H, d, J = 8.4, H-3′,5′), 7.19 (1H, d, J = 8.4, H-6), 7.63 (1H, d, J = 8.4, H-5).

2-[(7-Methyl-2-oxo-2*H*-chromen-4-ylmethyl)amino]terephthalic Acid Dimethyl Ester (22). Yield 60%, $C_{21}H_{19}NO_6$, mp 258-259°C. IR spectrum (KBr, cm^{-1}): 3375, 1715, 1688, 1612, 1575, 1480, 1424, 1350, 1298, 1220, 1170. PMR spectrum: 2.41 (3H, s, Me-7), 3.82 (6H, 2s, Me_2-2′,5′), 5.00 (2H, s, CH_2-4), 6.60 (3H, s, H-3), 7.04 (1H, dd, J = 8.2, 2.2, H-6), 7.25 (1H, d, J = 8.2, H-8), 7.27 (1H, d, J = 8.2, H-5), 7.43 (1H, d, J = 2.1, H-6′), 7.71 (1H, dd, J = 8.4, 2.1, H-4′), 7.71 (1H, d, J = 8.4, H-3′).

4-[(2-Fluorophenylamino)methyl]-6-hydroxy-7-methylchromen-2-one (23). Yield 56%, $C_{17}H_{14}FNO_3$, mp 231-232°C. IR spectrum (KBr, cm^{-1}): 3256, 1714, 1688, 1612, 1556, 1480, 1424, 1342, 1296, 1232, 1160. PMR spectrum: 2.46 (3H, s, Me-7), 4.49 (2H, br.s, CH_2-4), 6.12 (3H, s, H-3), 6.20 (1H, br.s, NH), 7.14 (1H, s, H-5), 7.22 (1H, s, H-8), 6.58 (1H, d, J = 8.2, H-6′), 6.61 (1H, d, J = 8.2, H-5′), 6.93 (1H, t, J = 7.8, H-4′), 7.09 (1H, dd, J = 7.8, 12, H-3′), 9.75 (1H, s, OH-6).

4-[(3-Chlorophenylamino)methyl]-6-hydroxy-7-phenylchromen-2-one (24). Yield 60%, $C_{22}H_{16}ClNO_3$, mp 248-249°C. IR spectrum (KBr, cm^{-1}): 3416, 1724, 1684, 1610, 1532, 1462, 1390, 1282, 1198, 1100. PMR spectrum: 4.51 (2H,

br.s, CH_2-4), 6.27 (3H, s, NH), 7.47 (5H, m, Ph-7), 7.37 (1H, s, H-8), 7.30 (1H, s, H-5), 7.19 (1H, t, J = 8.1, H-2′), 9.99 (1H, s, OH-6).

6-Hydroxy-4-[(3-methoxyphenylamino)methyl]-7-methylchromen-2-one (25). Yield 75%, $C_{18}H_{17}NO_4$, mp 215-216°C. IR spectrum (KBr, cm^{-1}): 3321, 3115, 1725, 1674, 1565, 1521, 1441, 1324, 1210, 1168, 1112. PMR spectrum: 2.23 (3H, s, Me-7), 3.65 (3H, s, OMe-3′), 4.41 (2H, br.s, CH_2-4), 6.20 (4H, m, H-3,2′,4′,6′), 6.27 (1H, br.s, NH), 6.99 (1H, t, J = 8.1, H-5′), 7.13 (1H, s, H-8), 7.21 (1H, s, H-5), 9.72 (1H, s, OH-6).

4-[(4-Ethoxyphenylamino)methyl]-6-hydroxy-7-methylchromen-2-one (26). Yield 80%, $C_{19}H_{19}NO_4$, mp 225-226°C. IR spectrum (KBr, cm^{-1}): 3390, 3320, 1712, 1640, 1556, 1492, 1432, 1375, 1284, 1182, 1090. PMR spectrum: 1.35 (3H, t, J = 8.2, CH_3-4′), 4.07 (2H, q, J = 8.2, CH_2-4′), 2.24 (3H, s, Me-7), 7.06 (2H, d, J = 9.0, H-3′,5′), 7.22 (3H, s, H-3), 8.46 (1H, s, H-5), 8.80 (1H, s, H-8), 9.72 (1H, s, OH-6).

2-[(6-Hydroxy-2-oxo-7-phenyl-2*H*-chromen-4-ylmethyl)amino]benzoic Acid Methyl Ester (27). Yield 71%, $C_{24}H_{19}NO_5$, mp 198-199°C. IR spectrum (KBr, cm^{-1}): 3336, 3212, 1719, 1670, 1572, 1424, 1394, 1324, 1262, 1124, 1102. PMR spectrum: 3.85 (3H, s, Me-2′), 4.75 (2H, br.s, CH_2-4), 6.13 (1H, s, H-3), 6.69 (2H, m, H-4′,5′), 7.40 (5H, m, Ph-6), 8.16 (1H, t, J = 6, NH), 10.05 (1H, s, OH-6).

4-[(2,3-Dimethylphenylamino)methyl]-6-hydroxy-7-methylchromen-2-one (28). Yield 79%, $C_{19}H_{19}NO_3$, mp 205-207°C. IR spectrum (KBr, cm^{-1}): 3212, 1708, 1620, 1560, 1475, 1432, 1226, 1162, 1032. PMR spectrum: 2.20 (9H, 3s, Me-7, Me-2′,3′-), 4.48 (2H, br.s, CH_2-4), 5.58 (1H, t, J = 5.4, NH), 6.10 (3H, s, H-3), 6.19 (1H, d, J = 7.8, H-6′), 6.48 (1H, d, J = 7.5, H-4′), 6.83 (1H, t, J = 7.5, H-5′), 7.18 (1H, s, H-5), 7.21 (1H, s, H-8), 9.75 (1H, s, OH-6).

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