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MODIFIED COUMARINS. 7. SYNTHESIS AND BIOLOGICAL ACTIVITY OF MANNICH BASES OF SUBSTITUTED 7,8,9,10-TETRAHYDROBENZO[*c*]CHROMEN-6-ONES

Ya. L. Garazd,[1] T. N. Panteleimonova,[2] M. M. Garazd,[3] and V. P. Khilya[1]

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Condensation of 1- and 3-hydroxy-7,8,9,10-tetrahydrobenzo[c]chromen-6-ones with substituted 1,1-diaminomethanes produced Mannich bases containing a dialkylaminomethyl group in the 2- and 4-positions of 7,8,9,10-tetrahydrobenzo[c]chromen-6-one. Pharmacological screening of 2-chloro-3-hydroxy-4-(1-pyrrolidinylmethyl)-7,8,9,10-tetrahydro-6H-benzo[c]chromen-6-one in Wistar rats showed that it possesses low toxicity and acts as a stimulant of the central and peripheral nervous systems with indications of neuroleptic and tranquilizing activities.

Key words: coumarins, 7,8,9,10-tetrahydrobenzo[*c*]chromen-6-one, Mannich reaction, synthesis.

One of the alternate routes to the production of new biologically active compounds is the synthesis of analogs of natural bioregulators in order to increase the pharmacological activity, in particular, by forming several active centers in the molecule. An advantage of such compounds is that they have structures close to the biochemical structures of the living organism and cause significantly less side effects. Owing to the high biological activity of natural coumarins and their synthetic analogs, they provide a basis for producing new pharmacologically active compounds. The Mannich reaction is one method of chemical modification that introduces into a molecule a pharmacophoric base that can be converted to an ammonium salt and make the molecule soluble in aqueous systems. According to the literature [1, 2], the majority of aminomethylated coumarin derivatives act as central-nervous-system stimulants, barbiturate antagonists, anticonvulsives, analgesics, antipyretics, and anti-inflammatory agents.

We synthesized Mannich bases based on 1-hydroxy- and 3-hydroxy-7,8,9,10-tetrahydrobenzo[*c*]chromen-6-ones. Hydroxycoumarins **1**-**4**, which are necessary for further transformations, were prepared by Pechmann condensation of polyphenols (resorcinol, 2-methylresorcinol, 4-chlororesorcinol, orcin) and ethyl-2-oxocyclohexanecarboxylate in the presence of conc. H_2SO_4.

The reaction of a substrate, amine, and formaldehyde in alcohol with prolonged heating are considered the classical conditions for the Mannich reaction of hydroxy compounds based on the benzopyran skeleton [3]. In our opinion, a more convenient method for introducing the aminomethyl group into the benzopyran system is the use of substituted 1,1-diaminomethanes because such reactions have fast reaction rates and few side reactions [4, 5].

It is known that the position *ortho* to a hydroxyl is the most preferred for attack under Mannich-reaction conditions for all phenol derivatives. This is due to the reaction mechanism, according to which a H-bond is formed between the Mannich reagent and the substrate, after which the *o*-position is attacked [3].

The C-aminomethylation reaction is carried out by boiling hydroxycoumarins with substituted 1,1-diaminomethanes in absolute dioxane. The aminomethyl group adds to the 4-position of 7,8,9,10-tetrahydrobenzo[*c*]chromen-6-one upon reaction with coumarins **1** and **2**. For **3** and **4**, it is directed to the 2-position according to PMR spectroscopy.

1) Taras Shevchenko Kiev National University, Kiev, ul. Vladimirskaya, 64; 2) Gerontology Institute, Academy of Medical Sciences of the Ukraine, Kiev, ul. Vyshgorodskaya, 67; 3) Institute of Bioorganic and Petroleum Chemistry, National Academy of Sciences of the Ukraine, Kiev, ul. Murmanskaya, 1, e-mail: gmm@i.com.ua. Translated from Khimiya Prirodnykh Soedinenii, No. 6, pp. 422-427, November-December, 2002. Original article submitted November 18, 2002.

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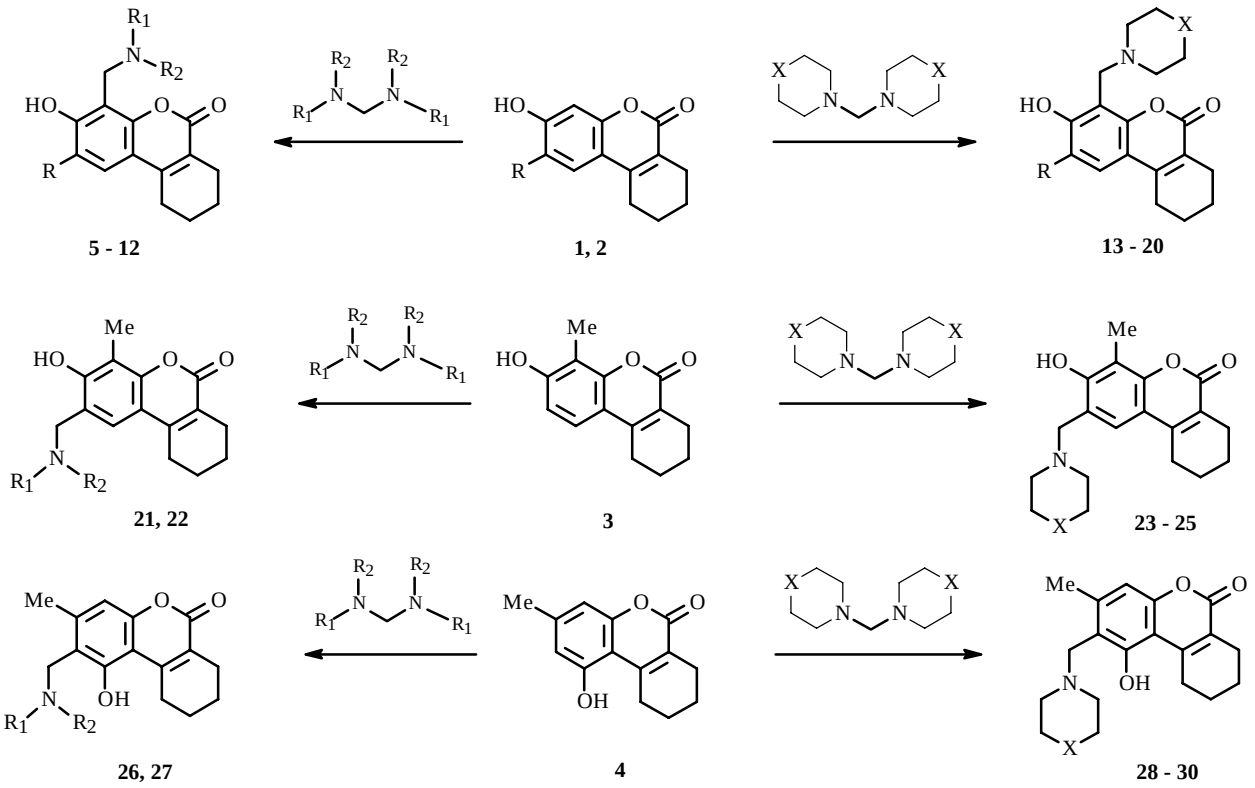

5 - 12 **1, 2** **13 - 20**

21, 22 **3** **23 - 25**

26, 27 **4** **28 - 30**

1: R = H; **2:** R = Cl; **5:** R = H, $R_1 = R_2 = CH_3$; **6:** R = Cl, $R_1 = R_2 = CH_3$; **7:** R = Cl, $R_1 = R_2 = CH_2CH_3$;
8: R = H, $R_1 = R_2 = (CH_2)_4$; **9:** R = Cl, $R_1 = R_2 = (CH_2)_4$; **10:** $R_1 = R_2 = CH_2CH(CH_3)CH_2CH_2$;
11: R = Cl, $R_1 = R_2 = CH_2CH(CH_3)CH_2CH_2$; **12:** R = Cl, $R_1 = R_2 = CH(CH_2CH_3)CH_2CH_2CH_2CH_2$;
13: R = H, $X = CH_2$; **14:** R = Cl, $X = CH_2$; **15:** R = H, $X = CH(CH_3)$; **16:** R = Cl, $X = CH(CH_3)$;
17: R = H, X = O; **18:** R = Cl, X = O; **19:** R = H, $X = NCH_3$; **21, 26:** $R_1 = R_2 = CH_3$;
22, 27: $R_1 = R_2 = (CH_2)_4$; **23**, **28**: $X = CH_2$; **24, 29:** $X = CH(CH_3)$; **25**, **30**: $X = NCH_3$

According to the results, the most active substrate in the aminomethylation reaction is 3-hydroxy-7,8,9,10-tetrahydro-6*H*-benzo[*c*]chromen-6-one (**1**), the reaction of which occurs within 0.5-1 h. Longer heating for 2-4 h is needed if 2-chloro derivative **2** is used. In our opinion, the low reactivity toward aminomethylation of the 2-position of 7,8,9,10-tetrahydro-6*H*-benzo[*c*]chromen-6-one proves that longer heating (5-10 h) is necessary to effect the Mannich reaction with the 4-methyl substituted derivative **3**. The activity of the 2-position increases significantly upon introducing a hydroxy in the 1-position because heating for 1-3 h is needed to complete the reaction for 1-hydroxy-3-methyl-7,8,9,10-tetrahydro-6*H*-benzo[*c*]chromen-6-one (**4**).

Aminals of dimethylamine (**5**, **6**, **21**, **26**), diethylamine (**7**), pyrrolidine (**8**, **9**, **22**, **27**), piperidine (**13**, **14**, **23**, **28**), 2-ethylpiperidine (**12**), 3-methylpiperidine (**10**, **11**), 4-methylpiperidine (**15**, **16**, **24**, **29**), morpholine (**17**, **18**), and 1-methylpiperazine (**19**, **20**, **25**, **30**) underwent the Mannich reaction. The most active of the 1,1-diaminomethanes was bis(dimethylamino)methane. Longer heating times are required if other aminals are used.

The structures of the Mannich bases were confirmed by quantitative elemental analysis and PMR spectroscopy. The PMR spectra of **5**-**20**, which contain a dialkylaminomethyl group in the 4-position, lack signals at 6.9-7.0 ppm for H-4 of 7,8,9,10-tetrahydrobenzo[*c*]chromen-6-one. Because H-4 does not couple, the spectrum is simplified for the aromatic protons. Protons H-1 and H-2 of **5**, **8**, **10**, **13**, **15**, **17**, and **19** resonate as doublets with spin—spin coupling constants (SSCC) 8.8 Hz at 7.35-7.38 and 6.72-6.75 ppm, respectively. For 2-chloro derivatives **6**, **7**, **9**, **11**, **12**, **14**, **16**, **18**, and **20**, H-1 is observed at 7.44-7.48 ppm as a 1-H singlet. An analogous trend is noted for 2-dialkylaminomethyl derivatives **21**-**30**. Proton H-1 in PMR spectra of Mannich bases **21**-**25** appears as a singlet at 7.00-7.03 ppm; for 1-hydroxy-3-methyl isomers **26**-**30**, H-4 resonates as a singlet at 6.57-6.58 ppm. The PMR spectra of **5**-**30** also contain 2H signals for the methylene and signals typical of dialkylamine

substituents. The methylene group of 4-dialkylaminomethyl derivatives **5-11** and **13-20** appears as a singlet at 4.01-4.23 ppm; for **21-30**, which contain the dialkylaminomethyl group in the 2-position, the methylene singlet occurs at stronger field, 3.67-3.87 ppm. It is noteworthy that the methylene protons in **12** are diastereotopic, as a result of which they appear as two doublets with SSCC 16.0 Hz. Hydroxyl protons OH-1 and OH-3 resonate at weak field (9.00-11.90 ppm) because they participate in stable intramolecular H-bonds with the N atom of the dialkylaminomethyl group.

Preliminary pharmacological screening of 2-chloro-3-hydroxy-4(1-pyrrolidinylmethyl)-7,8,9,10-tetrahydro-6*H*-benzo[*c*]chromen-6-one (**9**) carried out with Wistar rats showed that it possesses low toxicity, LD_{50} = 2500 mg/kg. Compound **9** acts as a stimulant of the central and peripheral nervous systems with indications of neuroleptic and tranquilizing activity. This Mannich base at a dose of 50 mg/kg increases by 65% the duration of narcotic sleep induced by hexenal and has no effect on nicotinic hyperkinesis, i.e., possesses cholinolytic properties.

Thus, preliminary pharmacological screening shows that derivatives of 7,8,9,10-tetrahydro-6*H*-benzo[*c*]chromen-6-one are promising for further investigations in the search for new biologically active compounds.

EXPERIMENTAL

The course of reactions and purity of products were monitored by TLC on Merck 60 F254 plates using $CHCl_3$—CH_3OH (9:1) and hexane—ethylacetate (7:3). IR and UV spectra were measured on a Nicolet FTIR Nexus-475 spectrometer and a Specord M40 spectrophotometer, respectively. PMR spectra were recorded on Varian VXR-300 and Varian Mercury-400 spectrometers at 300 and 400 MHz, respectively, relative to TMS (internal standard). Elemental analyses of all compounds agreed with those calculated.

3-Hydroxy-7,8,9,10-tetrahydro-6*H*-benzo[*c*]chromen-6-one (1). A cooled (0°C) solution of resorcinol (11.0 g, 0.1 mole) and ethyl-2-oxocyclohexanecarboxylate (16.0 mL, 0.1 mole) in ethanol (20 mL) was vigorously stirred, cooled, treated dropwise with conc. H_2SO_4 (10 mL), stirred until thickened, and left overnight at room temperature. The mixture was poured into icewater (250 mL). The resulting precipitate was filtered off and crystallized from propan-2-ol. Yield 16.42 g (76%), $C_{13}H_{12}O_3$, mp 205-206°C {lit. 185°C (dec.) [6], 201-202°C [7], 203-204°C [8, 9], 206-208°C [10], 210°C [11]}. IR spectrum (KBr, cm^{-1}): 3217, 2941, 1682, 1618, 1565, 1512, 1462, 1390, 1317, 1298, 1267, 1161, 1150, 1101, 1042, 854, 756. UV spectrum (dioxane, λ_{max}, nm, log ε): 219 (4.40), 291 (4.07), 319 (4.29). PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.70 (4H, m, CH_2-8, CH_2-9), 2.35 (2H, m, CH_2-10), 2.66 (2H, m, CH_2-7), 6.65 (1H, d, J = 2.1, H-4), 6.75 (1H, dd, J = 2.1, J = 8.7, H-2), 7.45 (1H, d, J = 8.7, H-1), 10.00 (1H, br.s, OH-3).

2-Chloro-3-hydroxy-7,8,9,10-tetrahydro-6*H*- benzo[*c*]chromen-6-one (2). Prepared analogously to **1** from 4-chlororesorcinol (14.46 g, 0.1 mole) and ethyl-2-oxocyclohexanecarboxylate (16.0 mL, 0.1 mole), yield 19.80 g (79%), $C_{13}H_{11}ClO_3$, mp 251-252°C (lig. 240-242°C [12]). IR spectrum (KBr, cm^{-1}): 3316, 2938, 1698, 1600, 1426, 1401, 1291, 1268, 1247, 1116, 1033, 872. UV spectrum (EtOH, λ_{max}, nm, log ε): 207 (4.72), 226 (4.39), 328 (4.26). PMR spectrum (300 MHz, DMSO-d_6, δ, ppm): 1.71 (4H, m, CH_2-8, CH_2-9), 2.36 (2H, m, CH_2-10), 2.65 (2H, m, CH_2-7), 6.86 (1H, s, H-4), 7.69 (1H, s, H-1), 10.00 (1H, br.s, OH-3).

3-Hydroxy-4-methyl-7,8,9,10-tetrahydro-6*H*-benzo[c]chromen-6-one (3). Prepared analogously to **1**, from 2-methylresorcinol (12.41 g, 0.1 mole) and ethyl-2-oxocyclohexanecarboxylate (16.0 mL, 0.1 mole), yield 19.34 g (84%), $C_{14}H_{14}O_3$, mp 272-273°C (lit. 268°C [13], 279-281°C [14]). IR spectrum (KBr, cm^{-1}): 3274, 2932, 1676, 1607, 1581, 1507, 1421, 1375, 1313, 1266, 1249, 1147, 1102, 805, 759. UV spectrum (EtOH, λ_{max}, nm, log ε): 204 (4.70), 225 (4.22), 324 (4.18). PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.72 (4H, m, CH_2-8, CH_2-9), 2.16 (3H, s, CH_3-4), 2.39 (2H, m, CH_2-10), 2.72 (2H, m, CH_2-7), 6.82 (1H, d, J = 8.7, H-2), 7.34 (1H, d, J = 8.7, H-1), 10.10 (1H, br.s, OH-3).

1-Hydroxy-3-methyl-7,8,9,10-tetrahydro-6*H*-benzo[c]chromen-6-one (4). Prepared analogously to **1** from orcin monohydrate (14.22 g, 0.1 mole) and ethyl-2-oxocyclohexanecarboxylate (16.0 mL, 0.1 mole), yield 14.05 g (61%), $C_{14}H_{14}O_3$, mp 228-229°C (lit. 243-245°C [15]). IR spectrum (KBr, cm^{-1}): 3308, 2947, 1677, 1621, 1600, 1512, 1430, 1386, 1361, 1277, 1094, 1035, 829. UV spectrum (dioxane, λ_{max}, nm, log ε): 212 (4.60), 245 (4.04), 255 (4.02), 298 (4.26). PMR spectrum (300 MHz, DMSO-d_6, δ, ppm): 1.67 (4H, m, CH_2-8, CH_2-9), 2.26 (3H, s, CH_3-3), 2.38 (2H, m, CH_2-10), 3.08 (2H, m, CH_2-7), 6.56 and 6.58 (2H, two s, H-2, H-4), 10.28 (1H, br.s, OH-1).

General Method for Synthesizing Mannich Bases 5-30. A solution of coumarin **1-4** (4 mmole) in absolute dioxane (30 mL) was treated with the appropriate substituted 1,1-diaminomethane (5 mmole). The reaction mixture was held at 100°C

for 0.5-10 h (completion of reaction determined by TLC). After the reaction was complete, solvent was removed in vacuum. The solid or oily product was crystallized from hexane—propan-2-ol (3:1).

4-[(Dimethylamino)methyl]-3-hydroxy-7,8,9,10-tetrahydro-6*H*-benzo[c]chromen-6-one (5). Yield 81%, $C_{16}H_{19}NO_3$, mp 161-162°C. IR spectrum (KBr, cm^{-1}): 3411, 2953, 1712, 1627, 1606, 1499, 1384, 1290, 1240, 1084, 1068, 1013, 815. UV spectrum (EtOH, λ_{max}, nm, log ε): 206 (4.84), 224 (4.39), 328 (4.33), 342 (4.22). PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.82 (4H, m, CH_2-8, CH_2-9), 2.43 [6H, s, $N(CH_3)_2$], 2.54 (2H, m, CH_2-10), 2.74 (2H, m, CH_2-7), 4.01 (2H, s, CH_2-4), 6.75 (1H, d, J = 8.8, H-2), 7.37 (1H, d, J = 8.8, H-1), 11.10 (1H, s, OH-3).

2-Chloro-4-[(dimethylamino)methyl]-3-hydroxy-7,8,9,10-tetrahydro-6*H*-benzo[c]chromen-6-one (6). Yield 88%, $C_{16}H_{18}ClNO_3$, mp 155-156°C. IR spectrum (KBr, cm^{-1}): 3393, 2944, 1708, 1623, 1598, 1477, 1390, 1358, 1300, 1246, 1103, 1056, 1015, 998, 758. UV spectrum (EtOH, λ_{max}, nm, log ε): 212 (4.67), 362 (4.19). PMR spectrum (400 MHz, $CDCl_3$, δ, ppm): 1.81 (4H, m, CH_2-8, CH_2-9), 2.43 [6H, s, $N(CH_3)_2$], 2.54 (2H, m, CH_2-10), 2.70 (2H, m, CH_2-7), 4.05 (2H, s, CH_2-4), 7.47 (1H, s, H-1), 11.81 (1H, s, OH-3).

2-Chloro-4-[(diethylamino)methyl]-3-hydroxy-7,8,9,10-tetrahydro-6*H*-benzo[c]chromen-6-one (7). Yield 75%, $C_{18}H_{22}ClNO_3$, mp 156-157°C. IR spectrum (KBr, cm^{-1}): 3400, 2938, 1713, 1622, 1596, 1479, 1415, 1387, 1295, 1271, 1097, 1042, 870, 754. UV spectrum (EtOH, λ_{max}, nm, log ε): 212 (4.52), 358 (4.13). PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.18 (6H, t, J = 7.2, two CH_3-2′), 1.82 (4H, m, CH_2-8, CH_2-9), 2.53 (2H, m, CH_2-10), 2.69 (2H, m, CH_2-7), 2.75 (4H, q, two CH_2-1′), 4.16 (2H, s, CH_2-4), 7.45 (1H, s, H-1), 11.90 (1H, s, OH-3).

3-Hydroxy-4-(1-pyrrolidinylmethyl)-7,8,9,10-tetrahydro-6*H*-benzo[c]chromen-6-one (8). Yield 81%, $C_{18}H_{21}NO_3$, mp 132-133°C. IR spectrum (KBr, cm^{-1}): 3397, 2940, 1714, 1626, 1604, 1496, 1386, 1284, 1243, 1084, 1067, 1044, 808. UV spectrum (dioxane, λ_{max}, nm, log ε): 225 (4.15), 322 (4.20). PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.82 (4H, m, CH_2-8, CH_2-9), 1.88 (4H, m, CH_2-3′, CH_2-4′), 2.54 (2H, m, CH_2-10), 2.74 (6H, m, CH_2-7, CH_2-2″, CH_2-5′), 4.18 (2H, s, CH_2-4), 6.74 (1H, d, J = 8.8, H-2), 7.36 (1H, d, J = 8.8, H-1), 9.70 (1H, s, OH-3).

2-Chloro-3-hydroxy-4-(1-pyrrolidinylmethyl)-7,8,9,10-tetrahydro-6*H*-benzo[c]chromen-6-one (9). Yield 83%, $C_{18}H_{20}ClNO_3$, mp 196-197°C. IR spectrum (KBr, cm^{-1}): 3434, 2935, 1703, 1584, 1478, 1427, 1398, 1328, 1292, 1261, 1242, 1175, 1100, 1038, 869, 753. UV spectrum (EtOH, λ_{max}, nm, log ε): 212 (4.64), 366 (4.26). PMR spectrum (400 MHz, $CDCl_3$, δ, ppm): 1.82 (4H, m, CH_2-8, CH_2-9), 1.92 (4H, m, CH_2-3′, CH_2-4′), 2.53 (2H, m, CH_2-10), 2.70 (2H, m, CH_2-7), 2.80 (4H, m, CH_2-2″, CH_2-5′), 4.23 (2H, s, CH_2-4), 7.46 (1H, s, H-1), 9.16 (1H, s, OH-3).

3-Hydroxy-4-[(3-methylpiperidino)methyl]-7,8,9,10-tetrahydro-6*H*-benzo[c]chromen-6-one (10). Yield 76%, $C_{20}H_{25}NO_3$, mp 156°C. IR spectrum (KBr, cm^{-1}): 3410, 2935, 1714, 1625, 1601, 1491, 1385, 1289, 1091, 1065, 1040, 811. UV spectrum (EtOH, λ_{max}, nm, log ε): 204 (4.71), 226 (4.21), 320 (4.25). PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.89 (3H, t, J = 6.0, CH_3-3′), 0.95 (1H, m, CH_2-4′α), 1.62 (1H, m, H-3′), 1.70-1.84 (9H, m, CH_2-8, CH_2-9, CH_2-5′, CH_2-4′β, CH_2-2′α, CH_2-6′α), 2.54 (2H, m, CH_2-10), 2.74 (2H, m, CH_2-7), 2.91 (2H, m, CH_2-2′β, CH_2-6′β), 4.02 (2H, s, CH_2-4), 6.74 (1H, d, J = 8.7, H-2), 7.34 (1H, d, J = 8.7, H-1), 10.43 (1H, s, OH-3).

2-Chloro-3-hydroxy-4-[(3-methylpiperidino)methyl]-7,8,9,10-tetrahydro-6*H*-benzo[c]chromen-6-one (11). Yield 80%, $C_{20}H_{24}ClNO_3$, mp 183-184°C. IR spectrum (KBr, cm^{-1}): 3405, 2932, 1715, 1622, 1597, 1478, 1415, 1385, 1294, 1101, 1049, 968, 754. UV spectrum (EtOH, λ_{max}, nm, log ε): 212 (4.53), 354 (4.09). PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.89 (3H, t, J = 5.6, CH_3-3′), 0.95 (1H, m, CH_2-4′α), 1.68 (1H, m, H-3′), 1.73-1.85 (9H, m, CH_2-8, CH_2-9, CH_2-5′, CH_2-4′β, CH_2-2′α, CH_2-6′α), 2.53 (2H, m, CH_2-10), 2.69 (2H, m, CH_2-7), 2.94 (2H, m, CH_2-2′β, CH_2-6′β), 4.05 (2H, s, CH_2-4), 7.45 (1H, s, H-1), 9.90 (1H, s, OH-3).

2-Chloro-3-hydroxy-4-[(2-ethylpiperidino)methyl]-7,8,9,10-tetrahydro-6*H*-benzo[c]chromen-6-one (12). Yield 73%, $C_{21}H_{26}ClNO_3$, mp 165-166°C. IR spectrum (KBr, cm-1): 3411, 2939, 1716, 1624, 1596, 1473, 1383, 1295, 1268, 1100, 1044, 967, 753. UV spectrum (EtOH, λ_{max}, nm, log ε): 212 (4.64), 358 (4.20). PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.94 (3H, t, J = 7.6, CH_3-2″), 1.44-1.83 (13H, m, CH_2-8, CH_2-9, CH_2-3′, CH_2-4′, CH_2-5′, CH_2-6′α, CH_2-1″), 2.36 (1H, m, H-2′), 2.52 (2H, m, CH_2-10), 2.69 (2H, m, CH_2-7), 3.08 (1H, m, CH_2-6′β), 4.02 (1H, d, J = 16.0, CH_2-4α), 4.38 (1H, d, J = 16.0, CH_2-4β), 7.44 (1H, s, H-1), 10.70 (1H, s, OH-3).

3-Hydroxy-4-piperidinomethyl-7,8,9,10-tetrahydro-6*H*-benzo[c]chromen-6-one (13). Yield 76%, $C_{19}H_{23}NO_3$, mp 156-157°C (lit. 170°C [16]). IR spectrum (KBr, cm^{-1}): 3395, 2931, 1709, 1626, 1602, 1496, 1410, 1379, 1287, 1263, 1089, 1063, 1041, 989, 808, 758. UV spectrum (dioxane, λ_{max}, nm, log ε): 221 (4.22), 322 (4.17). PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.66 (6H, m, CH_2-3′, CH_2-4′, CH_2-5′), 1.82 (4H, m, CH_2-8, CH_2-9), 2.10-2.20 (2H, m, CH_2-2′α, CH_2-6′α), 2.54

(2H, m, CH_2-10), 2.74 (2H, m, CH_2-7), 2.80-2.95 (2H, m, CH_2-2′β, CH_2-6′β), 4.02 (2H, s, CH_2-4), 6.72 (1H, d, J = 8.8, H-2), 7.35 (1H, d, J = 8.8, H-1), 10.80 (1H, s, OH-3).

2-Chloro-3-hydroxy-4-piperidinomethyl-7,8,9,10-tetrahydro-6*H*-benzo[c]chromen-6-one (14). Yield 89%, $C_{19}H_{22}ClNO_3$, mp 195-196°C. IR spectrum (KBr, cm^{-1}): 3404, 2943, 1711, 1622, 1597, 1478, 1384, 1339, 1294, 1266, 1098, 1046, 755. UV spectrum (EtOH, λ_{max}, nm, log ε): 212 (4.77), 352 (4.31). PMR spectrum (400 MHz, $CDCl_3$, δ, ppm): 1.71 (6H, m, CH_2-3′, CH_2-4′, CH_2-5′), 1.81 (4H, m, CH_2-8, CH_2-9), 2.10-2.20 (2H, m, CH_2-2′α, CH_2-6′α), 2.54 (2H, m, CH_2-10), 2.71 (2H, m, CH_2-7), 2.80-2.95 (2H, m, CH_2-2′β, CH_2-6′β), 4.07 (2H, s, CH_2-4), 7.46 (1H, s, H-1), 11.00 (1H, s, OH-3).

3-Hydroxy-4-[(4-methylpiperidino)methyl]-7,8,9,10-tetrahydro-6*H*-benzo[c]chromen-6-one (15). Yield 83%, $C_{20}H_{25}NO_3$, mp 142-143°C. IR spectrum (KBr, cm^{-1}): 3396, 2924, 1709, 1603, 1496, 1381, 1287, 1264, 1086, 1063, 1045, 972, 808, 758. UV spectrum (EtOH, λ_{max}, nm, log ε): 205 (4.75), 225 (4.24), 322 (4.30). PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.95 (3H, t, J = 6.4, CH_3-4′), 1.30 (2H, m, CH_2-3′α, CH_2-5′α), 1.47 (1H, m, H-4′), 1.70 (2H, m, CH_2-3′β, CH_2-5′β), 1.82 (4H, m, CH_2-8, CH_2-9), 2.21 (2H, m, CH_2-2′α, CH_2-6′α), 2.54 (2H, m, CH_2-10), 2.74 (2H, m, CH_2-7), 2.98 (2H, m, CH_2-2′β, CH_2-6′β), 4.03 (2H, s, CH_2-4), 6.72 (1H, d, J = 8.8, H-2), 7.35 (1H, d, J = 8.8, H-1), 11.15 (1H, s, OH-3).

2-Chloro-3-hydroxy-4-[(4-methylpiperidino)methyl]-7,8,9,10-tetrahydro-6*H*-benzo[c]chromen-6-one (16). Yield 85%, $C_{20}H_{24}ClNO_3$, mp 152-153° C. IR spectrum (KBr, cm^{-1}): 3414, 2928, 1721, 1597, 1481, 1418, 1384, 1342, 1298, 1263, 1101, 1048, 971, 868, 754. UV spectrum (dioxane, λ_{max}, nm, log ε): 212 (4.72), 230 (4.40), 329 (4.29). PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.95 (3H, t, J = 6.4, CH_3-4′), 1.34 (2H, m, CH_2-3′α, CH_2-5′α), 1.48 (1H, m, H-4′), 1.71 (2H, m, CH_2-3′β, CH_2-5′β), 1.82 (4H, m, CH_2-8, CH_2-9), 2.30 (2H, m, CH_2-2′α, CH_2-6′α), 2.53 (2H, m, CH_2-10), 2.69 (2H, m, CH_2-7), 3.02 (2H, m, CH_2-2′β, CH_2-6′β), 4.07 (2H, s, CH_2-4), 7.45 (1H, s, H-1), 11.60 (1H, s, OH-3).

3-Hydroxy-4-morpholinomethyl-7,8,9,10-tetrahydro-6*H*-benzo[c]chromen-6-one (17). Yield 91%, $C_{18}H_{21}NO_4$, mp 146-147°C (lit. 183-187°C [2], 190°C [16]). IR spectrum (KBr, cm^{-1}): 3432, 2928, 1706, 1606, 1496, 1411, 1384, 1348, 1288, 1238, 1116, 1086, 866, 760. UV spectrum (dioxane, λ_{max}, nm, log ε): 223 (4.33), 324 (4.26). PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.82 (4H, m, CH_2-8, CH_2-9), 2.54 (2H, m, CH_2-10), 2.63 (4H, m, CH_2-2′, CH_2-6′), 2.74 (2H, m, CH_2-7), 3.77 (4H, m, CH_2-3′, CH_2-5′), 4.06 (2H, s, CH_2-4), 6.75 (1H, d, J = 8.8, H-2), 7.38 (1H, d, J = 8.8, H-1), 10.50 (1H, s, OH-3).

2-Chloro-3-hydroxy-4-morpholinomethyl-7,8,9,10-tetrahydro-6*H*-benzo[c]chromen-6-one (18). Yield 89%, $C_{18}H_{20}ClNO_4$, mp 204-205°C. IR spectrum (KBr, cm^{-1}): 3432, 2943, 1706, 1626, 1598, 1474, 1408, 1386, 1304, 1290, 1116, 1101, 1052, 868, 756. UV spectrum (EtOH, λ_{max}, nm, log ε): 210 (4.72), 228 (4.38), 329 (4.28). PMR spectrum (400 MHz, $CDCl_3$, δ, ppm): 1.82 (4H, m, CH_2-8, CH_2-9), 2.54 (2H, m, CH_2-10), 2.70 (6H, m, CH_2-7, CH_2-2′, CH_2-6′), 3.79 (4H, m, CH_2-3′, CH_2-5′), 4.09 (2H, s, CH_2-4), 7.48 (1H, s, H-1), 10.10 (1H, s, OH-3).

3-Hydroxy-4-[(4-methylpiperazino)methyl]-7,8,9,10-tetrahydro-6*H*-benzo[c]chromen-6-one (19). Yield 86%, $C_{19}H_{24}N_2O_3$, mp 139-140°C (lit. 144-146°C [2]). IR spectrum (KBr, cm^{-1}): 3402, 2941, 1712, 1627, 1602, 1500, 1383, 1298, 1283, 1241, 1095, 1068, 1008, 820. UV spectrum (EtOH, λ_{max}, nm, log ε): 205 (4.97), 225 (4.49), 324 (4.48). PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.82 (4H, m, CH_2-8, CH_2-9), 2.31 (3H, s, NCH_3), 2.40-2.80 (4H, m, CH_2-2′, CH_2-3′, CH_2-5′, CH_2-6′), 2.54 (2H, m, CH_2-10), 2.73 (2H, m, CH_2-7), 4.07 (2H, s, CH_2-4), 6.73 (1H, d, J = 8.8, H-2), 7.36 (1H, d, J = 8.8, H-1), 9.60 (1H, s, OH-3).

2-Chloro-3-hydroxy-4-[(4-methylpiperazino)methyl]-7,8,9,10-tetrahydro-6*H*-benzo[c]chromen-6-one (20). Yield 82%, $C_{19}H_{23}ClN_2O_3$, mp 186-187°C. IR spectrum (KBr, cm^{-1}): 3413, 2937, 1721, 1597, 1479, 1458, 1384, 1346, 1300, 1101, 1048, 1005, 868, 818, 753. UV spectrum (EtOH, λ_{max}, nm, log ε): 210 (4.69), 229 (4.35), 333 (4.22). PMR spectrum (400 MHz, $CDCl_3$, δ, ppm): 1.81 (4H, m, CH_2-8, CH_2-9), 2.32 (3H, s, NCH_3), 2.40-2.80 (4H, m, CH_2-2′, CH_2-3′, CH_2-5′, CH_2-6′), 2.52 (2H, m, CH_2-10), 2.71 (2H, m, CH_2-7), 4.09 (2H, s, CH_2-4), 7.46 (1H, s, H-1), 9.50 (1H, s, OH-3).

2-[(Dimethylamino)methyl]-3-hydroxy-4-methyl-7,8,9,10-tetrahydro-6*H*-benzo[c]chromen-6-one (21). Yield 86%, $C_{17}H_{21}NO_3$, mp 162-163°C. IR spectrum (KBr, cm^{-1}): 3425, 2934, 1704, 1616, 1593, 1476, 1394, 1312, 1256, 1185, 1125, 1025, 963, 760. UV spectrum (EtOH, λ_{max}, nm, log ε): 209 (4.63), 227 (4.19), 328 (4.19). PMR spectrum (400 MHz, $CDCl_3$, δ, ppm): 1.78 (4H, m, CH_2-8, CH_2-9), 2.28 (3H, s, CH_3-4), 2.37 [6H, s, $N(CH_3)_2$], 2.54 (2H, m, CH_2-10), 2.70 (2H, m, CH_2-7), 3.85 (2H, s, CH_2-2), 7.00 (1H, s, H-1), 11.50 (1H, s, OH-3).

3-Hydroxy-4-methyl-2-(1-pyrrolydinylmethyl)-7,8,9,10-tetrahydro-6*H*-benzo[c]chromen-6-one (22). Yield 78%, $C_{19}H_{23}NO_3$, mp 149-150°C. IR spectrum (KBr, cm^{-1}): 3448, 2936, 1702, 1612, 1460, 1420, 1396, 1312, 1187, 1171, 1124, 1071, 881, 790. UV spectrum (EtOH, λ_{max}, nm, log ε): 209 (4.64), 227 (4.20), 329 (4.20). PMR spectrum (400 MHz, $CDCl_3$, δ, ppm): 1.82 (4H, m, CH_2-8, CH_2-9), 1.87 (4H, m, CH_2-3′, CH_2-4′), 2.28 (3H, s, CH_3-4), 2.54 (2H, m, CH_2-10), 2.65 (4H, m, CH_2-2′, CH_2-5′), 2.72 (2H, m, CH_2-7), 3.87 (2H, s, CH_2-2), 7.02 (1H, s, H-1), 11.00 (1H, s, OH-3).

3-Hydroxy-4-methyl-2-piperidinomethyl-7,8,9,10-tetrahydro-6*H*-benzo[c]chromen-6-one (23). Yield 76%, $C_{20}H_{25}NO_3$, mp 164-165°C. IR spectrum (KBr, cm^{-1}): 3448, 2935, 1703, 1615, 1597, 1421, 1397, 1312, 1279, 1186, 1126, 1036, 787. UV spectrum (CH_3CN, λ_{max}, nm, log ε): 209 (4.79), 227 (4.34), 329 (4.35). PMR spectrum (400 MHz, $CDCl_3$, δ, ppm): 1.65 (6H, m, CH_2-3′, CH_2-4′, CH_2-5′), 1.81 (4H, m, CH_2-8, CH_2-9), 2.30 (3H, s, CH_3-4), 2.55 (2H, m, CH_2-10), 2.71 (2H, m, CH_2-7), 3.71 (2H, s, CH_2-2), 7.00 (1H, s, H-1), 9.80 (1H, s, OH-3).

3-Hydroxy-4-methyl-2-[(4-methylpiperidino)methyl]-7,8,9,10-tetrahydro-6*H*-benzo[c]chromen-6-one (24). Yield 76%, $C_{21}H_{27}NO_3$, mp 136-137°C. IR spectrum (KBr, cm^{-1}): 3433, 2932, 1700, 1612, 1597, 1458, 1393, 1373, 1312, 1262, 1160, 1127, 1072, 969, 759. UV spectrum (dioxane, λ_{max}, nm, log ε): 212 (4.76), 228 (4.38), 324 (4.33). PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.95 (3H, t, J = 6.4, CH_3-4′), 1.31 (2H, m, CH_2-3′α, CH_2-5′α), 1.45 (1H, m, H-4′), 1.68 (2H, m, CH_2-3′β, CH_2-5′β), 1.81 (4H, m, CH_2-8, CH_2-9), 2.12 (2H, m, CH_2-2′α, CH_2-6′α), 2.29 (3H, s, CH_3-4), 2.55 (2H, m, CH_2-10), 2.71 (2H, m, CH_2-7), 2.95 (2H, m, CH_2-2′β, CH_2-6′β), 3.73 (2H, s, CH_2-2), 7.00 (1H, s, H-1), 9.50 (1H, s, OH-3).

3-Hydroxy-4-methyl-2-[(4-methylpiperazino)methyl]-7,8,9,10-tetrahydro-6*H*-benzo[c]chromen-6-one (25). Yield 86%, $C_{20}H_{26}N_2O_3$, mp 162-163°C. IR spectrum (KBr, cm^{-1}): 3433, 2934, 1694, 1610, 1596, 1458, 1393, 1313, 1269, 1185, 1169, 1130, 1085, 1009, 918, 816. UV spectrum (EtOH, λ_{max}, nm, log ε): 209 (4.69), 227 (4.22), 328 (4.25). PMR spectrum (400 MHz, $CDCl_3$, δ, ppm): 1.82 (4H, m, CH_2-8, CH_2-9), 2.29 (3H, s, CH_3-4), 2.32 (3H, s, NCH_3), 2.40-2.80 (4H, m, CH_2-2′, CH_2-3′, CH_2-5′, CH_2-6′), 2.54 (2H, m, CH_2-10), 2.71 (2H, m, CH_2-7), 3.76 (2H, s, CH_2-2), 7.03 (1H, s, H-1), 9.20 (1H, s, OH-3).

2-[(Dimethylamino)methyl]-1-hydroxy-3-methyl-7,8,9,10-tetrahydro-6*H*-benzo[c]chromen-6-one (26). Yield 85%, $C_{17}H_{21}NO_3$, mp 160-161°C. IR spectrum (KBr, cm^{-1}): 3434, 2944, 1706, 1609, 1579, 1429, 1318, 1248, 1220, 1160, 1101, 1021, 890, 773. UV spectrum (dioxane, λ_{max}, nm, log ε): 215 (4.65), 233 (4.18), 262 (4.09), 299 (4.30). PMR spectrum (400 MHz, $CDCl_3$, δ, ppm): 1.74 (4H, m, CH_2-8, CH_2-9), 2.26 (3H, s, CH_3-3), 2.35 [6H, s, $N(CH_3)_2$], 2.55 (2H, m, CH_2-10), 3.20 (2H, m, CH_2-7), 3.67 (2H, s, CH_2-2), 6.58 (1H, s, H-4), 11.00 (1H, s, OH-1).

1-Hydroxy-3-methyl-2-(1-pyrrolidinylmethyl)-7,8,9,10-tetrahydro-6*H*-benzo[c]chromen-6-one (27). Yield 76%, $C_{19}H_{23}NO_3$, mp 145-146°C. IR spectrum (KBr, cm^{-1}): 3434, 2934, 1690, 1622, 1601, 1459, 1411, 1379, 1338, 1150, 1116, 1073, 1046, 868. UV spectrum (dioxane, λ_{max}, nm, log ε): 218 (4.55), 235 (4.14), 259 (4.03), 299 (4.23). PMR spectrum (400 MHz, $CDCl_3$, δ, ppm): 1.74 (4H, m, CH_2-8, CH_2-9), 1.88 (4H, m, CH_2-3′, CH_2-4′), 2.26 (3H, s, CH_3-3), 2.55 (2H, m, CH_2-10), 2.68 (4H, m, CH_2-2′, CH_2-5′), 3.21 (2H, m, CH_2-7), 3.85 (2H, s, CH_2-2), 6.57 (1H, s, H-4), 9.90 (1H, s, OH-1).

1-Hydroxy-3-methyl-2-piperidinomethyl-7,8,9,10-tetrahydro-6*H*-benzo[c]chromen-6-one (28). Yield 81%, $C_{20}H_{25}NO_3$, mp 141-142°C. IR spectrum (KBr, cm^{-1}): 3424, 2946, 1697, 1621, 1602, 1463, 1415, 1383, 1198, 1150, 1114, 1041, 987, 860. UV spectrum (dioxane, λ_{max}, nm, log ε): 218 (4.48), 237 (4.00), 258 (3.93), 301 (4.17). PMR spectrum (400 MHz, $CDCl_3$, δ, ppm): 1.65 (6H, m, CH_2-3′, CH_2-4′, CH_2-5′), 1.75 (4H, m, CH_2-8, CH_2-9), 2.25 (3H, s, CH_3-3), 2.55 (2H, m, CH_2-10), 2.90-3.10 (4H, m, CH_2-2′, CH_2-5′), 3.19 (2H, m, CH_2-7), 3.68 (2H, s, CH_2-2), 6.57 (1H, s, H-4), 9.50 (1H, s, OH-1).

1-Hydroxy-3-methyl-2-[(4-methylpiperidino)methyl]-7,8,9,10-tetrahydro-6*H*-benzo[c]chromen-6-one (29). Yield 79%, $C_{21}H_{27}NO_3$, mp 149-150°C. IR spectrum (KBr, cm^{-1}): 3434, 2928, 1704, 1620, 1601, 1452, 1416, 1343, 1148, 1108, 1071, 972, 820. UV spectrum (dioxane, λ_{max}, nm, log ε): 218 (4.52), 237 (4.08), 258 (3.97), 301 (4.17). PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.96 (3H, t, J = 6.4, CH_3-4′), 1.30 (2H, m, CH_2-3′α, CH_2-5′α), 1.44 (1H, m, H-4′), 1.68 (2H, m, CH_2-3′β, CH_2-5′β), 1.75 (4H, m, CH_2-8, CH_2-9), 2.10 (2H, m, CH_2-2′α, CH_2-6′α), 2.25 (3H, s, CH_3-3), 2.55 (2H, m, CH_2-10), 2.99 (2H, m, CH_2-2′β, CH_2-6′β), 3.21 (2H, m, CH_2-7), 3.69 (2H, t, CH_2-2), 6.57 (1H, s, H-4), 9.20 (1H, s, OH-1).

1-Hydroxy-3-methyl-2-[(4-methylpiperazino)methyl]-7,8,9,10-tetrahydro-6*H*-benzo[c]chromen-6-one (30). Yield 74%, $C_{20}H_{26}N_2O_3$, mp 179-180°C. IR spectrum (KBr, cm^{-1}): 3449, 2930, 1700, 1619, 1604, 1460, 1415, 1351, 1415, 1352, 1286, 1151, 1111, 1093, 1011, 959, 821. UV spectrum (dioxane, λ_{max}, nm, log ε): 218 (4.60), 237 (4.18), 258 (4.09), 298 (4.27). PMR spectrum (400 MHz, $CDCl_3$, δ, ppm): 1.74 (4H, m, CH_2-8, CH_2-9), 2.26 (3H, s, CH_3-3), 2.32 (3H, s, NCH_3), 2.40-2.80 (4H, m, CH_2-2′, CH_2-3′, CH_2-5′, CH_2-6′), 2.54 (2H, m, CH_2-10), 3.19 (2H, m, CH_2-7), 3.72 (2H, s, CH_2-2), 6.58 (1H, s, H-4), 9.00 (1H, s, OH-1).

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