Synthesis of 4-aminopolymethoxycoumarins from 4-hydroxycoumarin triflates

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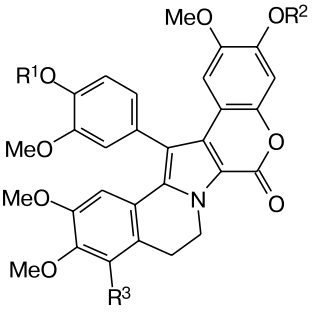
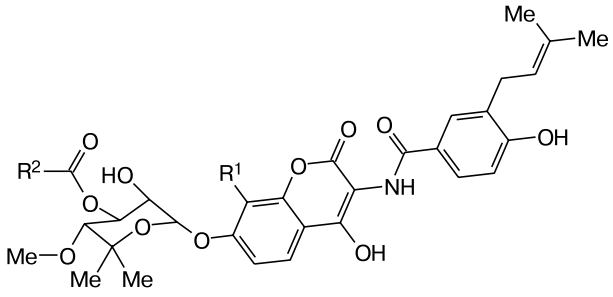
4-Aminocoumarins were synthesized in high yields by the reaction of 4-hydroxycoumarin trifluoromethanesulfonates with amines.

Key words: amines, 4-hydroxycoumarin trifluoromethanesulfonates, 4-aminocoumarins.

Nitrogen-containing coumarin derivatives isolated from different plant and animal sources, as well as from microorganisms, exhibit a broad spectrum of biological activities.[1] For example, novobiocin and chlorobiocin are efficient antibiotics.[2] Lamellarins I and K from sea sponges have cytotoxic activity against tumor lines resistant to most of antitumor drugs.[3] Their structural analog, *viz.*, lamellarin α-20-sulfate, is an efficient HIV-1 integrase inhibitor in nontoxic concentrations of the active component.[4]



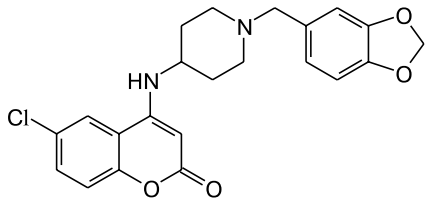
Lamellarin I: R^1 = H, R^2 = H, R^3 = OH
Lamellarin K: R^1 = Me, R^2 = H, R^3 = OH
Lamellarin α-20-sulfate: R^1 = H, R^2 = SO_2H, R^3 = H



Novobiocin: R^1 = H, R^2 = NH_2

Chlorobiocin: R^1 = Cl, R^2 = Me

4-Aminocoumarin derivative **1** proved to be a strong melanin-concentrating hormone receptor antagonist, which causes a dose-dependent weight loss.[5] 8-Piperazino- or 8-morpholino-7-hydroxycoumarins **2** possess high antiinflammatory activity.[6] 4-Morpholinocoumarin **3** is an efficient DNA-dependent protein kinase inhibitor.[7]



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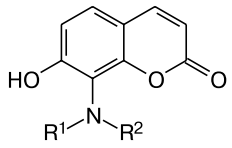

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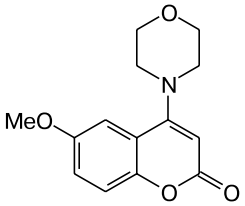

3

It should be noted that virtually all the above-mentioned compounds contain one or several hydroxy or methoxy groups, which is a prerequisite for biological activity.[1—5,8]

Results and Discussion

The aim of the present study was to synthesize new 4-aminopolymethoxycoumarins. *trans*-4-Amino-3-hydr-

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oxypiperidine derivatives are of particular interest because of their use in the synthesis of new therapeutical agents, which combine antiviral activity of hydroxylated piperidines, in particular, high anti-HIV activity,[9] with interesting biological properties of coumarins.[1] In addition, some 4-aryl-[10a] and 4-hetarylpolymethoxycoumarins[10b] prepared from hydroxycoumarin triflates exhibit considerable cytotoxic activity.[10a]

It is known that 4-aminocoumarins can be prepared from 4-halocoumarins.[11] However, the formation of the target products in these reactions occurs along with the α-pyrone ring opening accompanied by elimination of hydrogen halide. The reactions with 4-hydroxy analogs instead of 4-halocoumarins give considerable amounts of phenolic compounds as by-products.[12]

It should be noted that all these methods are applicable only to reactions of coumarins with primary amines and require the use of a considerable excess of amine (the amine : coumarin ratio should be 10 : 1—20 : 1). As a rule, the reactions are performed in glacial acetic acid, and isolation of the target products is a laborious procedure.[13]

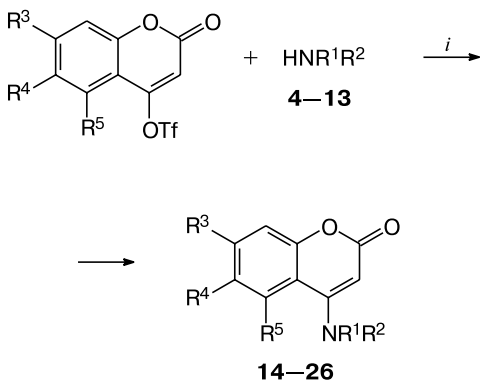
Amination of coumarins under microwave irradiation[13] gave good results only for unsubstituted coumarins. The reactions with 2,4,6-triisopropylbenzenesulfonates of hydroxycoumarins containing polar substituents afforded amination products in low yields.[7] Starting from hydroxycoumarin triflates, the target products were obtained in high yields only for coumarins containing electron-withdrawing substituents, the presence of the methoxy groups substantially decreased the yield of 4-aminocoumarins.[5] Data on functionalization of polymethoxycoumarins are virtually lacking.

We modified and optimized the reactions of amines **4—13** with hydroxycoumarin trifluoromethanesulfonates[5] (the use of pyridine as a base, refluxing in dioxane, the triflate : amine molar ratio was 1 : 1.3) (Scheme 1, Table 1).

Amination of 4-hydroxydimethoxy- and 4-hydroxytrimethoxycoumarin triflates with aliphatic amines and *p*-anisidine for 30 min afforded compounds **14—21** in almost quantitative yields (Table 1, entries *1—8*). The time of the reactions of substituted piperidines **9—13** was up to 4 h (see Table 1, entries *9—13*). The use of potassium phosphate instead of pyridine (entries *9—13*) facilitated isolation of the final products and made it possible to perform reactions with amine hydrochlorides. At room temperature, the same yields of the reaction products were obtained after 3—8 h.

trans-4-Amino-3-hydroxypiperidines **11—13** were prepared by regio- and stereoselective opening of 1-benzyl-3,4-epoxypiperidine **27** (see Ref. 14) with secondary amines in MeCN in the presence of 1 equiv. of anhydrous $LiClO_4$ at room temperature for 48 h followed by hydrogenolysis of *trans*-4-amino-1-benzyl-3-hydroxypiperidines **28a—c** (Scheme 2). Study by GLC-mass spectrometry demonstrated that aminolysis of epoxide **27** afforded only one amino alcohol. The *trans* structures of amino alcohols **28a—c** were determined by ^{1}H NMR spectroscopy. The coupling constants $J_{3,4} \approx 10$ Hz correspond to the diaxial orientation of the protons at the C(3) and

Scheme 1



Reagents and conditions: *i*. Base, dioxane, 100 °C.

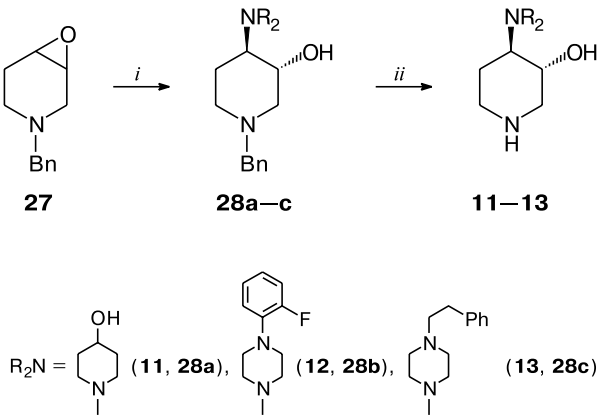
$R^3 = R^4 = R^5 = H$ (**14**, **17**), OMe (**15**, **16**, **19**, **21—26**);
$R^3 = R^5 = OMe$, $R^4 = H$ (**18**, **20**)

Table 1. Amination products of 4-hydroxycoumarin triflates

Entry	Amine HNR^1R^2	NR^1R^2	Product	Yield (%)
1	**4**	NEt_2	**14**	91
2	**4**	NEt_2	**15**	94
3	**5**		**16**	95
4	**6**		**17**	93
5	**6**		**18**	90
6	**6**		**19**	92
7	**7**		**20**	92
8	**8**		**21**	87
9	**9**		**22**	98
10	**10**		**23**	97
11	**11**		**24**	89
12	**12**		**25**	92
13	**13**		**26**	90

C(4) atoms of the piperidine ring and, consequently, the diequatorial orientation of the 4-amino and 3-hydroxy groups. The *trans* configuration of amino alcohols **11—13** formed by hydrogenolysis of *N*-benzyl derivatives **28a—c** retained, which was confirmed by the coupling constants $J_{3,4} \approx 12$ Hz.

Scheme 2



Reagents: *i*. R_2NH, MeCN, $LiClO_4$; *ii*. H_2 or $HCOONH_4$, Pd/C, MeOH.

4-Aminocoumarins **15**, **16**, and **18—26** and piperidines **11—13** and **28a—c** were synthesized for the first time.

To summarize, we developed an efficient procedure for the synthesis of 4-aminopolymethoxycoumarins in virtually quantitative yields.

Experimental

The NMR spectra were recorded on a Bruker Avance-400 spectrometer; the chemical shifts are given on the δ scale relative to $(Me_3Si)_2O$. The GLC-mass spectra were obtained on a Thermo Finnigan SSQ 7000 spectrometer. The MALDI TOF mass spectra were recorded on a Bruker Daltonics Proflex III spectrometer. 4-Hydroxycoumarin derivatives and the corresponding triflates were prepared according to known procedures.[15] 1-(2-Fluorophenyl)- and 1-phenethylpiperazine were purchased from Aldrich; 4- and 3-hydroxypiperidines were purchased from Fluka.

***trans*-1-Benzyl-3-hydroxy-4-(4-phenethylpiperazin-1-yl)piperidine trihydrochloride (28c).** Anhydrous $LiClO_4$ (0.140 g, 1.32 mmol) was added to a solution of 1-benzyl-3,4-epoxypiperidine (**27**) (0.250 g, 1.32 mmol) in anhydrous MeCN (2.5 mL), and the reaction mixture was stirred until complete dissolution was achieved. 1-Phenethylpiperazine (0.250 g, 1.32 mmol) was added to the resulting solution, and the mixture was stirred at ~20 °C for 48 h (TLC monitoring). Then water (3 mL) was added to the reaction mixture, acetonitrile was evaporated, the product was extracted with CH_2Cl_2 (5×2 mL), the combined organic extracts were dried with anhydrous Na_2SO_4, and the solution was concentrated. The residue (0.490 g) was dissolved in anhydrous ethanol (10 mL) and a saturated solution of hydrogen chloride in anhydrous ethanol was added to pH 4. The solvent was evaporated. The resulting product was dried *in vacuo* over KOH and P_2O_5 and recrystallized form anhydrous ethanol. The crystals were washed with diethyl ether and dried *in vacuo*. *trans*-1-Benzyl-3-hydroxy-4-(4-phenethylpiperazin-1-yl)piperidine trihydrochloride (**28c**) was obtained in a yield of 0.600 g (97%) as a colorless crystalline compound, t.decomp. 260—261 °C (EtOH). Found (%): C, 58.71; N, 8.44; H 7.38. $C_{24}H_{36}N_3OCl_3$. Calculated (%): C, 58.96; N, 8.59; H, 7.42. ^{1}H NMR ($CDCl_3$, δ), for the free base:* 1.54 (dq, 1 H, $H_a(5)$, $^2J_{5a,5e}$ = 12.4 Hz, $^3J_{5a,6a}$ = 11.9 Hz, $^3J_{5a,6e}$ = 3.8 Hz, $^3J_{5a,4}$ = 12.1 Hz); 1.72 (m, 1 H, $H_e(5)$, $^2J_{5a,5e}$ = 12.4 Hz); 1.89 (t, 1 H, $H_a(2)$, $^2J_{2a,2e}$ = 10.1 Hz, $^3J_{2a,3}$ = 9.6 Hz); 1.97 (dt, 1 H, $H_a(6)$, $^2J_{6a,6e}$ = 11.3 Hz, $^3J_{6,5}$ = 11.9 Hz, $^3J_{6a,5e}$ = 2.2 Hz); 2.21 (ddd, 1 H, H(4), $^3J_{4,5a}$ = 12.1 Hz, $^3J_{4,3}$ = 10.1 Hz, $^3J_{4,5e}$ = 3.5 Hz); 2.44—2.63 (m, 8 H), 2.75—2.84 (m, 4 H), 2.93 (m, 1 H, $H_e(6)$, $^2J_{6,6}$ = 11.3 Hz); 3.24 (ddd, 1 H, $H_e(2)$, $^2J_{2a,2e}$ = 10.1 Hz, $^3J_{2e,3}$ = 4.3 Hz, $^4J_{2e,6e}$ = 1.5 Hz); 3.49 (br.s, 1 H, 3-OH); 3.53 (AB system, 2 H, $PhC\underline{H}_2$); 3.59 (dt, 1 H, H(3), $^3J_{3,4}$ = 10.1 Hz, $^3J_{3,2a}$ = 9.6 Hz, $^3J_{3,2e}$ = 4.3 Hz); 7.16—7.33 (m, 10 H, 2 Ph). ^{13}C NMR ($CDCl_3$), δ: 21.51 (C(5)); 33.62 ($Ph\underline{C}H_2CH_2$); 48.34 (2 C, piperazine ring); 52.91 (C(6)); 53.69 (2 C, piperazine ring); 58.82, 60.44, 62.66, 65.94 ($PhCH_2\underline{C}H_2$, C(2), C(4), C(6), $Ph\underline{C}H_2N$); 68.94 (C(3)); 126.00, 127.02, 128.12 (2 C); 128.33 (2 C); 128.59 (2 C); 129.05 (2 C); 138.01, 140.20 (2 Ph).

***trans*-1-Benzyl-4-[4-(2-fluorophenyl)piperazin-1-yl]-3-hydroxypiperidine (28b)** was prepared analogously from 1-benzyl-3,4-epoxypiperidine (**27**) (0.500 g, 2.65 mmol) and 1-(2-fluorophenyl)piperazine (0.480 g, 2.65 mmol). The yield of the free base was 0.940 g (96%). A colorless crystalline compound, m.p. 123—124 °C (EtOH). Found (%): C, 71.68, 71.40; N, 11.41, 11.22; H, 7.40, 7.50. $C_{22}H_{28}N_3OF$. Calculated (%): C, 71.52; N, 11.37; H, 7.64. ^{1}H NMR ($CDCl_3$), δ: 1.61 (dq, 1 H, $H_a(5)$, $^2J_{5a,5e}$ = 12.5 Hz, $^3J_{5a,6a}$ = 11.7 Hz, $^3J_{5a,6e}$ = 3.8 Hz, $^3J_{5a,4}$ = 12.0 Hz); 1.78 (m, 1 H, $H_e(5)$, $^2J_{5e,5a}$ = 12.5 Hz); 1.93 (t, 1 H, $H_a(2)$, $^3J_{2a,2e}$ = 10.1 Hz, $^2J_{2a,3}$ = 10.0 Hz); 2.02 (dt, 1 H, $H_a(6)$, $^2J_{6a,6e}$ = 11.4 Hz, $^3J_{6a,5a}$ = 11.7 Hz, $^3J_{6a,5e}$ = 1.8 Hz); 2.28 (ddd, 1 H, H(4), $^3J_{4,5a}$ = 12.0 Hz, $^3J_{4,3}$ = 9.9 Hz, $^3J_{4,5e}$ = 3.8 Hz); 2.58—2.66 (m, 2 H, piperazine); 2.89—3.00 (m, 3 H, piperazine, $H_e(6)$); 3.11 (m, 4 H, piperazine); 3.24 (ddd, 1 H, $H_e(2)$, $^2J_{2e,2a}$ = 10.1 Hz, $^3J_{2e,3}$ = 4.5 Hz, $^4J_{2e,6e}$ = 1.5 Hz); 3.52 (br.s, 1 H, 3-OH); 3.57 (AB system, 2 H, $PhC\underline{H}_2$, ^2J = 13.9 Hz); 3.65 (dt, 1 H, H(3), $^3J_{3,4}$ = 9.9 Hz, $^3J_{3,2a}$ = 10.0 Hz, $^3J_{3,2e}$ = 4.5 Hz); 6.90—7.08 (m, 4 H, FPh); 7.22—7.34 (m, 5 H, Ph). ^{13}C NMR ($CDCl_3$), δ: 21.62 (C(5)); 48.42 (2 C, piperazine); 50.99 (2 C, piperazine); 52.81, 58.69, 62.55, 65.86 (C(2), C(4), C(6), $Ph\underline{C}H_2N$); 69.03 (C(3)); 116.01 (d, 1 C, $\underline{C}_6H_4F$, J = 20.5 Hz); 118.91 (s, 1 C, $\underline{C}_6H_4F$); 122.48 (d, 1 C, $\underline{C}_6H_4F$, J = 8.1 Hz); 124.39 (s, 1 C, $\underline{C}_6H_4F$); 127.10 (Ph); 128.16 (2 C, Ph); 129.08 (2 C, Ph); 137.72 (Ph); 139.94 (d, 1 C, $\underline{C}_6H_4F$, J = 8.1 Hz); 155.63 (d, 1C, $\underline{C}_6H_4F$, J = 245.9 Hz).

***trans*-1-Benzyl-3-hydroxy-4-(4-hydroxypiperidino)piperidine dihydrochloride (28a)** was prepared analogously from 1-benzyl-3,4-epoxypiperidine (**27**) (0.500 g, 2.65 mmol) and 4-hydroxypiperidine (0.270 g, 2.65 mmol) in a yield of 0.780 g (81%) as

* Hereinafter, free bases were isolated as follows: hydrochloride (0.060 g) was dissolved in water (2 mL), alkalified with NaOH to pH 12, and extracted with CH_2Cl_2 (5×1 mL). The extract was dried with anhydrous Na_2SO_4, and the solvent was removed *in vacuo*.

a colorless crystalline compound, m.p. 217—218 °C (with decomp., EtOH). Found (%): C, 56.00; N, 7.56; H, 7.92. $C_{17}H_{28}N_2O_2Cl_2$. Calculated (%): C, 56.20; N, 7.71; H, 7.77. ^{1}H NMR ($CDCl_3$), δ for the free base: 1.44—1.63 (m, 3 H, H_a(5), 4-hydroxypiperidine ring); 1.63 (m, 1 H, H_e(5), $^2J_{5e,5a}$ = 12.6 Hz); 1.83—1.93 (m, 4 H, H_a(2), $^2J_{2a,2e}$ = 10.2 Hz, $^3J_{2a,3}$ = 9.9 Hz, 4-hydroxypiperidine ring, O<u>H</u>); 1.97 (dt, 1 H, H_a(6), $^2J_{6a,6e}$ = 11.6 Hz, $^3J_{6a,5a}$ = 11.6 Hz, $^2J_{6a,5e}$ = 2.5 Hz); 2.14—2.20 (m, 2 H, H_a(4), 4-hydroxypiperidine ring); 2.54—2.65 (m, 2 H, 4-hydroxypiperidine ring); 2.84—2.95 (m, 2 H, H_e(6), 4-hydroxypiperidine ring); 3.21 (ddd, 1 H, H_e(2), $^2J_{2e,2a}$ = 10.2 Hz, $^3J_{2e,3}$ = 4.6 Hz, $^4J_{2e,6e}$ = 2.0 Hz); 3.52 (br.s, 1 H, OH); 3.53 (AB system, 2 H, PhC<u>H</u>$_2$, ^2J = 12.9 Hz); 3.57 (dt, 1 H, H(3), $^3J_{3,4}$ = 9.6 Hz); 3.67 (m, 1 H, 4′-H (4-hydroxypiperidine ring)); 7.21—7.33 (m, 5 H, Ph). ^{13}C NMR ($CDCl_3$), δ: 21.56 (C(5)); 34.99, 35.17 (4-hydroxypiperidine ring); 44.32, 48.05 (4-hydroxypiperidine ring); 52.94, 58.79, 62.66, 66.13, 67.94 (C(2), C(4), C(6), Ph<u>C</u>H$_2$, C(4′) (4-hydroxypiperidine ring)); 69.16 (C(3)); 127.04, 128.14 (2 C), 129.09 (2 C), 137.91 (Ph).

***trans*-3-Hydroxy-4-(4-hydroxypiperidin-1-yl)piperidine dihydrochloride (11).** 10% Pd/C (0.050 g) was added to a solution of compound **28a** (0.500 g, 1.72 mmol) in MeOH (25 mL) at ~20 °C, and a stream of H_2 was passed through the solution with vigorous stirring for 15 h (TLC monitoring). The catalyst was filtered off, and the solution was concentrated. The product (0.330 g) was dissolved in anhydrous ethanol (10 mL), and a saturated solution of hydrogen chloride in anhydrous ethanol was added to pH 4. The solvent was removed by evaporation, and the resulting dihydrochloride was dried *in vacuo* over KOH and P_2O_5. The precipitate was recrystallized from anhydrous ethanol and dried *in vacuo*. The yield was 0.420 g (90%). A colorless crystalline compound, m.p. 247—248 °C (EtOH). Found (%): C, 44.12; N, 10.04; H, 8.20. $C_{10}H_{22}N_2O_2Cl_2$. Calculated (%): C, 43.96; N, 10.25; H, 8.12. ^{1}H NMR ($CDCl_3$), δ for the free base: 1.38 (dq, 1 H, H_a(5), $^2J_{5a,5e}$ = 12.1 Hz, $^3J_{5a,6a}$ = 11.2 Hz, $^3J_{5a,6e}$ = 4.0 Hz, $^3J_{5a,4}$ = 12.4 Hz); 1.50 (m, 1 H, 4-hydroxypiperidine ring); 1.59 (m, 1 H, 4-hydroxypiperidine ring); 1.75 (m, 1 H, H_e(5), $^2J_{5e,5a}$ = 12.1 Hz); 1.88 (m, 2 H, 4-hydroxypiperidine ring), 2.19 (dt, 1 H, 4-hydroxypiperidine ring, J = 10.2 Hz, J = 10.2 Hz, J = 2.3 Hz); 2.31 (ddd, 1 H, H(4), $^3J_{4,5a}$ = 12.4 Hz, $^3J_{4,3}$ = 9.6 Hz, $^3J_{4,5e}$ = 3.5 Hz); 2.43 (t, 1 H, H_a(2), $^2J_{2a,2e}$ = 11.4 Hz, $^3J_{2a,3}$ = 9.5 Hz); 2.55 (dt, 1 H, H_a(6), $^2J_{6a,6e}$ = 12.2 Hz, $^3J_{6a,5a}$ = 11.2 Hz, $^2J_{6a,5e}$ = 2.0 Hz); 2.59—2.66 (m, 2 H, 4-hydroxypiperidine ring); 2.88 (m, 1 H, 4-hydroxypiperidine ring); 2.91 (br.s, 3 H, NH, 2 OH); 3.10 (m, 1 H, H_e(6), $^2J_{6e,6a}$ = 12.2 Hz); 3.34 (ddd, 1 H, H_e(2), $^2J_{2e,2a}$ = 11.4 Hz, $^3J_{2e,3}$ = 4.8 Hz, $^4J_{2e,6e}$ = 0.5 Hz); 3.57 (dt, 1 H, H(3), $^3J_{3,4}$ = 9.6 Hz, $^3J_{3,2a}$ = 9.5 Hz, $^3J_{3,2e}$ = 4.8 Hz); 3.64 (m, 1 H, 4′-H (4-hydroxypiperidine ring)). ^{13}C NMR ($CDCl_3$), δ: 23.34 (C(5)); 34.88, 35.07 (4-hydroxypiperidine ring); 44.13, 45.91, 48.06, 51.85 (4-hydroxypiperidine ring, C(2), C(6)); 67.06, 67.04, 69.14 (C(3), C(4), 4-hydroxypiperidine ring).

***trans*-4-[4-(2-Fluorophenyl)piperazin-1-yl]-3-hydroxypiperidine dihydrochloride (12)** was prepared analogously from compound **28b** (0.500 g, 1.36 mmol). The reaction time was 8 h. The yield was 0.440 g (92%). A colorless crystalline compound, m.p. 220—221 °C (with decomp., EtOH). Found (%): C, 51.30; N, 11.87; H, 6.96. $C_{15}H_{24}FN_3OCl_2$. Calculated (%): C, 51.14; N, 11.93; H, 6.87. ^{1}H NMR ($CDCl_3$), δ for the free base: 1.43 (dq, 1 H, H_a(5), $^2J_{5a,5e}$ = 12.4 Hz, $^3J_{5a,6a}$ = 11.2 Hz, $^3J_{5a,6e}$ = 4.0 Hz, $^3J_{5a,4}$ = 12.5 Hz); 1.82 (m, 1 H, H_e(5), $^2J_{5e,5a}$ = 12.4 Hz); 2.35 (ddd, 1 H, H(4), $^3J_{4,5a}$ = 12.5 Hz, $^3J_{4,3}$ = 9.8 Hz, $^3J_{4,5e}$ = 3.3 Hz); 2.45 (t, 1 H, H_a(2), $^3J_{2a,2e}$ = 10.5 Hz, $^2J_{2a,3}$ = 10.0 Hz); 2.57 (dt, 1 H, H_a(6), $^2J_{6a,6e}$ = 10.4 Hz, $^3J_{6a,5a}$ = 11.2 Hz, $^3J_{6a,5e}$ = 2.0 Hz); 2.58—2.65 (m, 2 H, piperazine ring); 2.82—2.95 (m, 2 H, piperazine ring); 3.02—3.18 (m, 5 H, piperazine ring, H_e(6)); 3.37 (dd, 1 H, H_e(2), $^2J_{2e,2a}$ = 10.5 Hz, $^3J_{2e,3}$ = 4.4 Hz); 3.40 (br.s, 2 H, NH, 3-OH); 3.48 (dt, 1 H, H(3), $^3J_{3,4}$ = 9.8 Hz, $^3J_{3,2a}$ = 10.0 Hz, $^3J_{3,2e}$ = 4.4 Hz); 6.89—7.09 (m, 4 H, F-Ph). ^{13}C NMR ($CDCl_3$), δ: 23.51 (C(5)); 46.03 (C(6)); 48.19 (2 C, piperazine ring); 50.92 (2 C, piperazine ring); 52.07, 66.96 (C(2), C(4)); 69.25 (C(3)); 115.89 (d, 1 C, <u>C</u>$_6$H$_4$F, J = 20.5 Hz); 118.77 (s, 1 C, <u>C</u>$_6$H$_4$F); 122.31 (d, 1 C, <u>C</u>$_6$H$_4$F, J = 7.3 Hz); 124.27 (d, 1 C, <u>C</u>$_6$H$_4$F, J = 2.9 Hz); 139.87 (d, 1 C, <u>C</u>$_6$H$_4$F, J = 8.1 Hz); 157.96 (d, 1 C, <u>C</u>$_6$H$_4$F, J = 245.9 Hz).

***trans*-3-Hydroxy-4-(4-phenethylpiperazin-1-yl)piperidine trihydrochloride (13).** Ammonium formate (0.330 g, 5.24 mmol) and 10% Pd/C (0.050 g) were added to a solution of compound **28c** (0.500 g, 1.31 mmol) in MeOH (25 mL). The reaction mixture was refluxed with stirring for 7 h. The catalyst was filtered off, the solvent was evaporated, a 20% NaOH solution (5 mL) was added, the product was extracted with CH_2Cl_2 (5×2 mL), and the combined organic extracts were dried with anhydrous Na_2SO_4. The solution was concentrated, the residue (0.360 g) was dissolved in anhydrous ethanol (10 mL), a saturated solution of hydrogen chloride in anhydrous ethanol was added to pH 4, the solvent was removed, and the residue was dried *in vacuo* over KOH and P_2O_5 and recrystallized from anhydrous ethanol. Compound **13** was obtained in a yield of 0.470 g (90%) as colorless crystals, t.decomp. 225—226 °C (EtOH). Found (%): C, 51.42; N, 10.70; H, 7.53. $C_{17}H_{30}N_3OCl_3$. Calculated (%): C, 51.20; N, 10.54; H, 7.58. ^{1}H NMR (DMSO-d_6), δ: 2.02 (m, 1 H, H_a(5)); 2.40 (m, 1 H, H_e(5)); 2.76 (m, 1 H, H(4)); 2.90 (m, 1 H, H_a(2)); 3.10 (m, 2 H, H_a(6), 3-OH); 3.28—3.44 (m, 4 H, H_e(2), H_e(6), PhC<u>H</u>$_2$); 3.47—3.93 (m, 10 H, piperazine ring, PhCH$_2$C<u>H</u>$_2$); 4.27 (m, 1 H, H(3)); 6.40 (br.s, 1 H, NH^+); 7.23—7.39 (m, 5 H, Ph); 9.61 (br.s, 2 H, NH_2^+); 12.15 (br.s, 1 H, NH^+). ^{13}C NMR (DMSO-d_6), δ: 21.29 (C(5)); 29.10 (Ph<u>C</u>H$_2$CH$_2$); 41.21, 45.01 (C(2), C(6)); 46.92 (2 C, piperazine ring); 48.09 (2 C, piperazine ring); 55.84, 62.34 (PhCH$_2$<u>C</u>H$_2$, C(4)); 64.76 (C(3)); 126.74, 128.53 (2 C), 128.65 (2 C), 136.69 (Ph).

Synthesis of compounds 14—21 (general procedure). Amine (0.17—0.22 mmol, 1.2 equiv.) was added to a mixture of 4-hydroxycoumarin triflate (0.13—0.17 mmol) and pyridine (0.39—0.51 mmol, 3 equiv.) in anhydrous dioxane (3 mL). The reaction mixture was stirred at 100 °C for 30 min. After removal of the solvent *in vacuo*, the products were isolated by column chromatography on silica gel with 3 : 2 ethyl acetate—light petroleum as an eluent.

4-Diethylaminochromen-2-one (14), yellow oil, the yield was 91%. ^{1}H NMR ($CDCl_3$), δ: 1.26 (t, 6 H, CH_3, J = 7.1); 3.41 (q, 4 H, CH_2, J = 7.1 Hz); 5.65 (s, 1 H, H(3)); 7.24 (t, 1 H, Ar, J = 7.6 Hz); 7.34 (d, 1 H, Ar, J = 8.3 Hz); 7.49 (t, 1 H, Ar, J = 7.6 Hz); 7.66 (d, 1 H, Ar, J = 8.0 Hz). ^{13}C NMR ($CDCl_3$), δ: 12.14 (CH_2<u>Me</u>); 45.48 (<u>C</u>H$_2$Me); 95.96 (C(3)); 116.99 (C(10)); 117.89 (C(8)); 123.10 (C(5)); 125.03 (C(6)); 131.19 (C(7)); 154.31 (C(9)); 159.36 (C(4)); 162.79 (C = O). Compound **14** has been synthesized earlier,[16] but was not completely characterized.

4-Diethylamino-5,6,7-trimethoxychromen-2-one (15), yellow oil, the yield was 94%. ^{1}H NMR ($CDCl_3$), δ: 1.15 (t, 6 H, Me,

J = 7.1 Hz); 3.31 (q, 4 H, CH_2, J = 7.1 Hz); 3.73, 3.89, and 3.90 (all s, 3 H each, OMe); 5.51 (s, 1 H, H(3)); 6.65 (s, 1 H, H(8)). ^{13}C NMR ($CDCl_3$), δ: 11.64, 45.58, 56.11, 61.54, 62.48, 94.16, 96.92, 105.00, 139.66, 150.30, 152.12, 155.90, 159.03, 162.63. MS (EI, 70 eV), m/z: 307 $[M]^+$, 292, 278, 264, 235, 208, 193, 164, 72.

5,6,7-Trimethoxy-4-piperidinochromen-2-one (16), yellow crystals, m.p. 142—143 °C, the yield was 95%. ^{1}H NMR ($CDCl_3$), δ: 1.66 (m, 2 H, CH_2); 1.76 (quint, 4 H, CH_2, J = 5.5 Hz); 3.10 (m, 4 H, CH_2), 3.80 (s, 3 H, OMe), 3.90 (s, 3 H, OMe), 3.91 (s, 3 H, OMe), 5.54 (s, 1 H, H(3)); 6.66 (s, 1 H, H(8)). ^{13}C NMR ($CDCl_3$), δ: 24.19, 25.60, 52.84, 56.11, 61.53, 62.78, 93.56, 96.96, 104.68, 139.70, 150.42, 152.10, 155.99, 161.62, 162.72. MS (EI, 70 eV), m/z: 319 $[M]^+$, 304, 289, 276, 250, 234, 208, 192, 160, 130, 95, 84, 77, 56, 44.

4-Morpholinochromen-2-one (17), yellow crystals, m.p. 143 °C (*cf*: m.p. 139—141 °C (see Ref. 17), 143—144 °C (see Ref. 7)), the yield was 93%. ^{1}H NMR ($CDCl_3$), δ: 3.25 (m, 4 H, CH_2); 3.93 (m, 4 H, CH_2); 5.73 (s, 1 H, H(3)); 7.25 (td, 1 H, H(6), J_1 = 7.7 Hz, J_2 = 1.1 Hz); 7.33 (dd, 1 H, H(8), J_1 = 8.0 Hz, J_2 = 0.9 Hz); 7.50 (td, 1 H, H(7), J_1 = 8.1 Hz, J_2 = 1.5 Hz); 7.61 (dd, 1 H, H(5), J_1 = 8.1 Hz, J_2 = 1.5 Hz). ^{13}C NMR ($CDCl_3$), δ: 51.48, 66.35, 98.20, 116.08, 117.84, 123.48, 124.63, 131.59, 154.25, 161.04, 162.22.

5,7-Dimethoxy-4-morpholinochromen-2-one (18), yellow crystals, m.p. 169—170 °C, the yield was 90%. ^{1}H NMR ($CDCl_3$), δ: 3.12 (m, 4 H, CH_2); 3.86 (s, 3 H, OMe) 3.87 (m, 4 H, CH_2); 3.89 (s, 3 H, OMe); 5.48 (s, 1 H, C(3)H); 6.32 (d, 1 H, H(6), J = 7.6 Hz); 6.48 (d, 1 H, H(8), J = 2.3 Hz). ^{13}C NMR ($CDCl_3$), δ: 51.80, 55.71, 56.18, 66.48, 92.74, 94.11, 95.86, 100.72, 157.04, 157.82, 161.33, 162.48, 162.70. MS (EI, 70 eV), m/z: 291 $[M]^+$, 260, 232, 220, 205, 178, 164, 149, 86, 69, 44, 32.

5,6,7-Trimethoxy-4-morpholinochromen-2-one (19), colorless crystals, m.p. 143—145 °C, the yield was 92%. ^{1}H NMR ($CDCl_3$), δ: 3.13 (m, 4 H, CH_2); 3.82 (s, 3 H, OMe); 3.86 (m, 4 H, CH_2); 3.88 and 3.90 (both s, 3 H each, OMe); 5.54 (s, 1 H, C(3)H); 6.66 (s, 1 H, CH(8)). ^{13}C NMR ($CDCl_3$), δ: 52.02, 56.17, 61.52, 62.90, 66.54, 94.23, 97.16, 104.10, 139.91, 149.97, 152.07, 156.31, 160.98, 162.29. MS (EI, 70 eV), m/z: 321 $[M]^+$, 307, 291, 279, 263, 235, 208, 177, 150, 134, 106, 86, 77, 69.

5,7-Dimethoxy-4-(4-methylpiperazin-1-yl)chromen-2-one (20), yellow crystals, m.p. 177—179 °C, the yield was 92%. Found (%): C, 63.20, 62.95; N, 9.31, 9.22; H, 6.82, 6.75. $C_{16}H_{20}N_2O_4$. Calculated (%): C, 63.14; N, 9.20; H, 6.62. ^{1}H NMR ($CDCl_3$), δ: 2.35 (s, 3 H, NCH_3,); 2.56 and 3.13 (both m, 4 H each, 2 CH_2); 3.82 and 3.87 (both s, 3 H each, OMe); 5.45 (s, 1 H, CH(3)); 6.29 (d, 1 H, CH(6), J = 2.3 Hz); 6.44 (d, 1 H, CH(8), J = 2.3 Hz). ^{13}C NMR ($CDCl_3$), δ: 46.04, 51.24, 54.60, 55.62, 56.12, 92.56, 94.09, 95.70, 100.94, 157.15, 157.76, 161.21, 162.51, 162.57. MS (EI, 70 eV), m/z: 304 $[M]^+$, 261, 256, 234, 222, 83, 70, 49, 43, 32.

4-(*p*-Anisidino)-5,6,7-trimethoxychromen-2-one (21), yellow crystals, m.p. 194—196 °C, the yield was 87%. Found (%): C, 63.81, 63.95; N, 3.98, 3.90; H, 5.30, 5.45. $C_{19}H_{19}NO_6$. Calculated (%): C, 63.86; N, 3.92; H, 5.36. ^{1}H NMR ($CDCl_3$), δ: 3.86, 3.90, and 3.94 (all s, 3 H each, OMe); 4.11 (s, 3 H, Me); 5.33 (s, 1 H, H(3)); 6.68 (s, 1 H, H(8)); 6.97 (d, 2 H, Ar, J = 8.0 Hz); 7.22 (d, 2 H, Ar, J = 8.0 Hz); 9.01 (br.s, 1 H, NH). ^{13}C NMR ($CDCl_3$), δ: 55.55, 56.19, 61.19, 62.22, 82.66, 97.10, 101.42, 114.90, 127.09, 130.29, 138.24, 150.60, 151.67, 154.97, 156.23, 158.23, 162.92.

Synthesis of compounds 22 and 23 (general procedure). Amine **9** or **10** (0.17 mmol, 1.3 equiv.) was added to a mixture of 4-hydroxy-5,6,7-trimethoxycoumarin triflate (0.13 mmol) and K_3PO_4 (0.39 mmol, 3 equiv.) in anhydrous dioxane (3 mL). The reaction mixture was stirred at 100 °C for 4 h, and the amination product was isolated by silica gel column chromatography (4 : 1 ethyl acetate—methanol mixture as the eluent).

4-(4-Hydroxypiperidino)-5,6,7-trimethoxychromen-2-one (22), yellow crystals, m.p. 173—175 °C, the yield was 98%. ^{1}H NMR ($CDCl_3$, CD_3OD), δ: 1.69—1.77 and 1.99—2.02 (both m, 2 H each, CH_2); 2.90 (s, 1 H, OH); 3.43—3.48 and 3.80—3.90 (both m, 2 H each, CH_2); 3.77, 3.86, and 3.90 (all s, 3 H each, OMe); 5.51 (s, 1 H, H(3)); 6.70 (s, 1 H, H(8)). ^{13}C NMR ($CDCl_3$, CD_3OD), δ: 33.46, 49.11, 49.24, 55.88, 61.15, 62.47, 92.30, 96.90, 104.36, 139.93, 150.33, 151.88, 156.54, 161.89, 164.12. MS (MALDI), m/z: 336.936 $[M + H]^+$; $[M + H]^+_{calc}$ 336.360.

4-(3-Hydroxypiperidino)-5,6,7-trimethoxychromen-2-one (23), yellow oil, the yield was 97%. ^{1}H NMR ($CDCl_3$, CD_3OD), δ: 1.46 (m, 1 H, CH_2); 1.74 (m, 2 H, CH_2); 1.91, 2.07, and 2.72 (all m, 1 H each, CH_2); 3.37 (s, 1 H, OH); 3.02 and 3.56 (both m, 1 H each, CH_2); 3.77 (s, 3 H, OMe); 3.87 (m, 1 H, CH_2); 3.88 and 3.91 (both s, 3 H each, OMe); 5.54 (s, 1 H, H(3)); 6.70 (s, 1 H, H(8)). ^{13}C NMR ($CDCl_3$, CD_3OD), δ: 22.78, 32.47, 51.94, 56.04, 58.23, 61.36, 62.58, 66.04, 92.69, 96.95, 105.25, 118.98, 135.25, 151.39, 156.48, 161.82, 163.23. MS (MALDI), m/z: 336.999 $[M + H]^+$; $[M + H]^+_{calc}$ 336.360.

Synthesis of compounds 24—26 (general procedure). Amine hydrochloride (0.17 mmol, 1.3 equiv.) was added to a mixture of 4-hydroxy-5,6,7-trimethoxycoumarin triflate (0.13 mmol) and K_3PO_4 (0.39 mmol, 3 equiv.) in anhydrous dioxane (3 mL). The reaction mixture was stirred at 100 °C for 4 h, and the amination product was isolated by silica gel column chromatography (4 : 1 ethyl acetate—methanol mixture as the eluent).

4-[4-(4-Hydroxypiperidino)-3-hydroxypiperidino]-5,6,7-trimethoxychromen-2-one (24), yellow oil, the yield was 89%. ^{1}H NMR ($CDCl_3$, CD_3OD), δ: 1.51—1.96 (m, 7 H, CH_2); 2.10, 2.27, 2.40, and 2.53 (all m, 1 H each, CH_2); 2.67 (m, 3 H, CH_2); 2.93 (m, 1 H, CH_2); 3.62 (m, 2 H, OH); 3.71 (m, 1 H, CH_2); 3.74 (s, 3 H, OMe); 3.80 (m, 1 H, CH_2); 3.87 and 3.88 (both s, 3 H each, OMe); 5.54 (s, 1 H, H(3)); 6.64 (s, 1 H, H(8)). ^{13}C NMR ($CDCl_3$, CD_3OD), δ: 21.64, 34.85, 35.03, 44.55, 47.79, 51.69, 56.17, 56.76, 61.55, 62.64, 65.72, 67.72, 68.89, 94.86, 97.05, 104.33, 131.11, 139.82, 150.28, 152.03, 156.29, 162.40. MS (MALDI), m/z: 435.512 $[M + H]^+$; $[M + H]^+_{calc}$ 435.491.

4-{4-[4-(2-Fluorophenyl)piperazin-1-yl]-3-hydroxypiperidino}-5,6,7-trimethoxychromen-2-one (25), yellow crystals, m.p. 202—204 °C, the yield was 90%. Found (%): C, 63.14; N, 8.25; H, 6.35. $C_{27}H_{32}N_3O_6F$. Calculated (%): C, 63.15; N, 8.18; H, 6.28. ^{1}H NMR ($CDCl_3$, CD_3OD), δ: 1.72—1.81 and 1.92—1.94 (both m, 1 H each, CH_2); 2.36—2.82 (m, 17 H, CH_2); 2.02 (s, 1 H, OH); 2.44—2.58 (m, 5 H, CH_2); 2.97—2.98 and 3.61—3.64 (both m, 2 H each, CH_2); 3.77 (s, 3 H, OMe); 3.79—3.85 (m, 1 H, CH_2); 3.88 and 3.89 (both s, 3 H each, OMe); 5.57 (s, 1 H, C(3)); 6.65 (s, 1 H, C(8)); 6.93—7.07 (m, 4 H, Ar). ^{13}C NMR ($CDCl_3$, CD_3OD), δ: 21.69, 48.50, 51.05, 51.61, 56.17, 56.73, 61.57, 62.70, 65.50, 68.74, 94.81, 94.02, 104.30, 116.01—116.21 (d, 1 S, J = 20.5 Hz); 118.99,

122.61—122.68 (d, 1 C, J = 7.3 Hz); 124.48, 139.78—139.88 (d, 1 C, J = 7.3 Hz); 139.96, 150.26, 152.02, 154.47—156.91 (d, 1 C, J = 248.2 Hz); 156.26, 162.34. MS (MALDI), m/z: 513.997; M_{calc} 513.558.

4-[3-Hydroxy-4-(4-phenethylpiperazin-1-yl)piperidino]-5,6,7-trimethoxychromen-2-one (26), yellow oil. The yield was 92%. Found (%): C, 66.37, 66.54; N, 8.08, 8.10; H, 7.15, 7.03. $C_{29}H_{37}N_3O_6$. Calculated (%): C, 66.52; N, 8.02; H, 7.12. ^{1}H NMR ($CDCl_3$, CD_3OD), δ: 1.67 and 1.86 (both m, 1 H each, CH_2); 2.36—2.82 (m, 17 H, CH_2); 3.21 (s, 1 H, OH); 3.57 (m, 1 H, CH_2); 3.64 (s, 2 H, OCH_2); 3.75 (m, 2 H, CH_2); 3.83 and 3.85 (both s, 3 H each, OMe); 5.51 (s, 1 H, H(3)); 6.63 (s, 1 H, H(8)); 7.14 (m, 3 H, CH); 7.23 (m, 2 H, CH). ^{13}C NMR ($CDCl_3$, CD_3OD), δ: 21.58, 33.59, 51.62, 53.63, 56.19, 56.75, 60.44, 61.64, 62.74, 65.48, 68.59, 94.97, 97.04, 104.31, 126.13, 128.43, 128.68, 139.78, 140.12, 150.25, 152.02, 156.26, 160.97, 162.48. MS (MALDI), m/z: 523.976; M_{calc} 523.621.

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