The First Synthesis of 3-Hydroxy-2-(polyfluoroalkyl)chromones and Their Ammonium Salts. 3-Hydroxychromone in the Mannich Reaction

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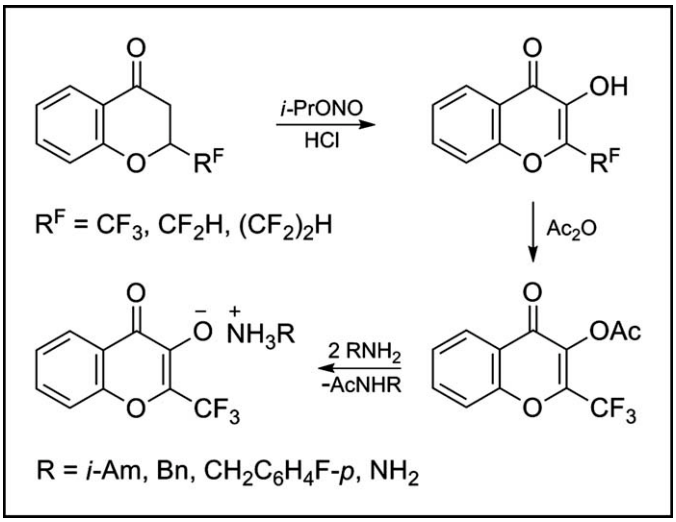

3-Hydroxy-2-(polyfluoroalkyl)chromones were obtained in good yields via the nitrozation reaction of 2-(polyfluoroalkyl)chroman-4-ones with isopropyl nitrite in the presence of hydrochloric acid. Treatment of 3-acetoxy-2-(trifluoromethyl)chromone with primary amines and hydrazine gave the corresponding ammonium salts. Reaction of 3-hydroxychromone, prepared by this method, with formaldehyde and α-aminoacids has been studied.

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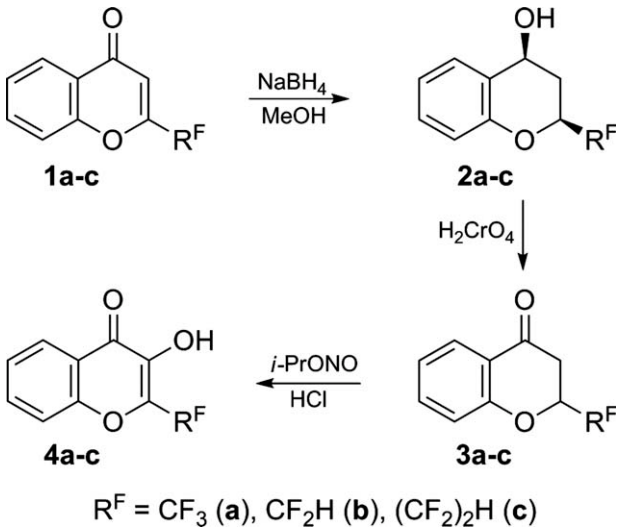
INTRODUCTION

The chromone ring is an integral part of many natural and biologically active substances. The biological potency of chromone derivatives and, in particular, halogen-containing chromones, has been widely documented [1,2]. Therefore, considerable efforts have been paid to explore new synthetic route to halogenated derivatives of chromone and to study their chemical properties. Polyfluoroalkyl groups, especially the CF_3 group, are highly important substituents in the field of organic chemistry. The introduction of these groups into organic molecules can bring about some remarkable changes in the physical properties, chemical reactivity, and biological activity of the derived fluorinated compounds [3]. Thus, it is well known that the insertion of polyfluoroalkyl substituents into the 2-position of chromones activates molecules of these compounds and reveals significant differences in the reactivity of 2-alkyl- and 2-(polyfluoroalkyl)chromones with respect to nucleophilic reagents [4]. The variety of the reactions of 2-R^F-chromones makes this class of compounds very useful for synthesis of R^F-containing heterocycles with potential biological activity [2].

However, to the best of our knowledge, very little is known about the synthesis and properties of 3-substituted 2-R^F-chromones. There have been only some papers on the preparation of 3-chloro- [5], 3-bromo- [6], 3-cyano- [7], 3-carbamoyl- [7], and 3-carbethoxychromones [8] with a R^F group at the 2-position. 2-(Polyfluoroalkyl)chromones containing electron-donating substituents at the 3-position had not been described yet. In view of the unique biological properties displayed by chromones [1,2] on one hand and by many fluorine-containing heterocycles [9] on the other hand, it was of interest to obtain 2-R^F-chromones with an electron-donating hydroxy group at the C-3 atom and their derivatives. It is worth to note that 3-hydroxyflavone is the most simple model of aglucones of polyhydroxyflavones

Scheme 1



which, linked by glucoside bond at the C-3 atom, are very widely spread heterocycles in the nature.

Recently [10], we have reported that reduction of readily available 2-(polyfluoroalkyl)chromones **1** with sodium borohydride provides a simple preparative procedure to *cis*-2-(polyfluoroalkyl)chroman-4-ols **2**, the oxidation of which to 2-(polyfluoroalkyl)chroman-4-ones **3** was performed with chromic acid in ethyl ether. We regarded these compounds as desirable targets because of their relationship to naturally occurring benzopyran derivatives and usefulness as R^F-containing building blocks for the preparation of more complex partially fluorinated heterocycles and other highly functionalized biologically and medicinally important products.

RESULTS AND DISCUSSION

Now we wish to report the successful nitrozation reaction of 2-R^F-chroman-4-ones **3** for the synthesis of previously unknown 3-hydroxy-2-(polyfluoroalkyl)chromones **4**. We found that treatment of an alcoholic solution of **3a–c** with an excess of isopropyl nitrite (3.0 equiv) and concentrated hydrochloric acid at 0–80°C for 3 h gave chromones **4a–c** in 42–68% yields as colorless crystals (Scheme 1). In the ^{1}H NMR spectra of these products in DMSO-d_6, a singlet at δ 10.4–10.7 ppm for the OH proton appeared in place of the disappearance of signals at δ 2.9–3.0 and 4.8–4.9 ppm associated with the C-3 methylene and C-2 methine protons of the starting 2-R^F-chroman-4-ones **3**. It was also observed that all protons of the benzene ring shifted to lower field and, hence, formation of the pyrone ring took place under the action of isopropyl nitrite.

To demonstrate the ability of compounds **4** to undergo alkylation and acylation reactions, chromone **4a** as a representative example was allowed to react with MeI and Ac_2O. Our results showed that **4a** smoothly reacts with an excess of MeI (refluxing acetone, K_2CO_3, 8 h) and Ac_2O (pyridine, ~20°C, 2 days) to produce the expected 3-methoxy- and 3-acetoxy-2-(trifluoromethyl)-chromones **5** and **6** in 87% and 77% yields, respectively (Scheme 2). The most notable feature in the ^{1}H NMR spectra of **5** and **6** is the absence of a signal of the hydroxy group and the appearance of singlets at δ 4.04 and 2.41 ppm due to the MeO and MeCO groups. Previously, their non-fluorinated analogs, 3-methoxy-, 3-acetoxy-, and 3-hydroxy-2-methylchromones, were obtained by reaction of ω-bromo-2-hydroxyacetophenone with acetic acid anhydride and sodium acetate [11]. The synthesis of 3-hydroxy-2-methylchromone has been also achieved by oxidation of 2-methylchroman-4-one with isoamyl nitrite [12].

It is known that reactions of 2-R^F-chromones **1** with amines and hydrazines proceed at the C-2 atom with pyrone ring opening to form β-aminovinylketones [13] and pyrazoles [14]. However, the acetylated derivative **6** did not show any analogous behavior to **1** and reacted with isoamyl-, benzyl-, and *p*-fluorobenzylamines in ethanol at room temperature immediately to give the corresponding salts **7a–c** as the sole isolated products in 47–85% yields. Similarly, reaction with hydrazine hydrate leads to hydrazinium 4-oxo-2-(trifluoromethyl)-4*H*-chromen-3-olate **7d** in 69% yield (Scheme 2). These salts are stable compounds and can be stored at room

Scheme 2

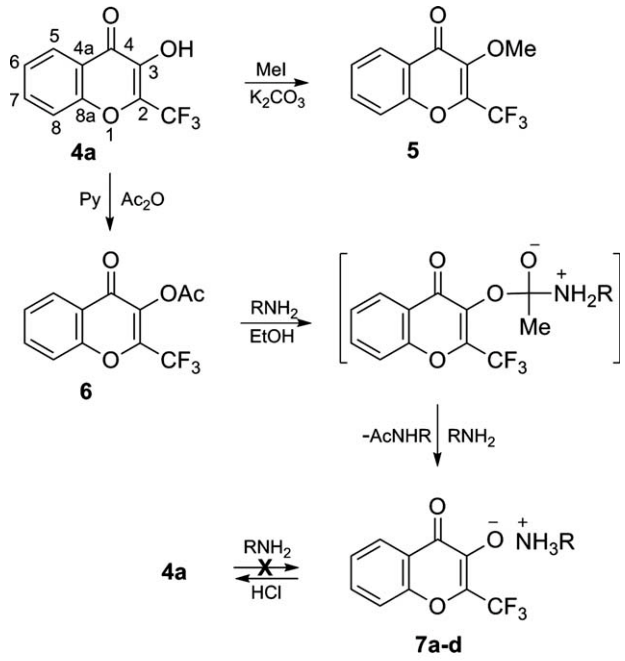


Table 1

Selected ^{13}C NMR data of chromones **1a** [16], **6**, **4a**, **7a**, and **8** [17a].

Chromone	Chemical shifts, δ (ppm)		
	C-2	C-3	C-4
1a[a]	152.2	110.4	176.8
6[a]	144.8	135.2	171.7
4a[b]	133.7	141.3	173.6
7a[b]	131.8	152.3	180.4
8[a]	139.9	142.1	174.0

[a] In $CDCl_3$.
[b] In DMSO-d_6.

temperature within several months. Thus, the salts formation was achieved without destruction of the chromone ring system. However, when an ethanolic solution of **4a** or **6** with benzylamine or hydrazine was heated, the reaction did not occur and only resinification was observed. Also, we were unable to obtain the corresponding salts from **6** and *tert*-butylamine, cyclohexylamine, and ethylenediamine. It should be noted that 3-hydroxychromone reacts with hydrazine hydrate in methanol to give 4-hydroxy-3-(2-hydroxyphenyl)-1*H*-pyrazole [15].

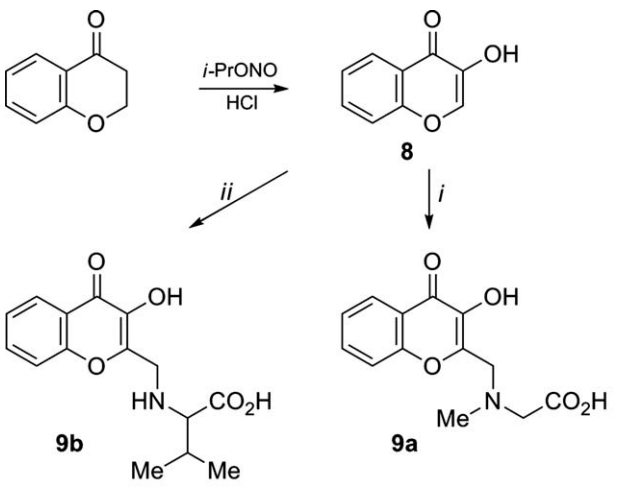
Reaction of the chromone derivative **6** with amines and hydrazine under mild conditions represents an easy access to the ammonium salts of 3-hydroxy-2-(trifluoromethyl)chromone **7a–d**, which could not be directly prepared from chromone **4a** and amines. The salts produced by this addition-elimination sequence gave the starting compound **4a** when treated by an ethanolic solution of hydrochloric acid at −30°C. The lack of chromone reactivity towards amines and hydrazine can be caused by the conjugation effect of the electron releasing OH and OAc groups, which decrease the electrophilic character of the C-2 atom, which is usually attacked first in the reaction of a chromone system with nucleophiles [2].

The IR spectra of **7a–d** display two distinct absorption bands at approximately 1630 and 1610 cm^{-1} assigned to the C=O and C=C functions, respectively, as in the case of the protonated form **4a**. In the ^1H NMR spectra of these compounds, the ammonium protons appeared as broad singlets within the range δ 3.0–7.2 ppm ($CDCl_3$). The ^{13}C spectra of compounds **7a,d** are much more informative and display low field signals at ca. δ 180.3, 154.2, and 152.1 ppm, which are assigned to C-4, C-8a, and C-3, respectively. The aromatic carbons fall within the range δ 118–133 ppm; the C-2 atom, adjacent to the CF_3 group, appeared as a quartet at δ 131.8–132.0 ppm ($^2J_{C,F}$ = 32.0 Hz), shifted upfield compared with C-2 of chromones **1**, **4**, and **6**. The ^1H-coupled ^{13}C NMR spectrum of **7a** was used to assign signals for the quaternary carbon atoms. The chemical shifts of the pyrone carbon atoms are presented in Table 1 to demonstrate the deshielding and shielding effects of the oxygen substituent at the 3-position on the C-3 and C-2 atoms compared with H-3 of chromone **1a**. As can been seen from Table 1, the appearance of the 3-OH group leads to considerable shielding of the C-2 atom, which is related to the lack of usual chromone reactivity.

Next, taking into account the above results and that the 3-hydroxychromone ring is an important structural fragment of many natural and biologically active substances [18], we decided to investigate the possibility of preparing 3-hydroxychromone **8** through nitrozation reaction of chroman-4-one under our reaction conditions. Previously, this compound was prepared by oxidation of chromone and 3-formylchromone using different reagents in two steps [17]. We found that the reaction between commercially available chroman-4-one and isopropyl nitrite is a useful method for the preparation of **8** because it requires only one step, cheap common reagents, and short reaction times (2–3 h in this case), albeit in only 35% yield (Scheme 3).

The replacement of a H-3 atom in 2- and 3-unsubstituted chromones by an alkyl- or dialkylaminomethyl group in the Mannich reaction is well known [19]. Very recently [20], it has been shown that 3-formylchromones react with α-aminoacids in the presence of excess formaldehyde to produce *N*-(chromone-3-ylmethyl)-α-aminoacids by a deformylative Mannich type reaction. It was also observed that α-aminoacids can be used as the amine component in a Mannich reaction with kojic acid [21]. However, the use of 3-hydroxychromones in this reaction has not been reported in the literature. Our preliminary results showed that 3-hydroxychromone **8** smoothly reacted with such α-aminoacids as sarcosine

Scheme 3



Reaction conditions: i, CH_2O, sarcosine; *ii*, CH_2O, valine

and valine in the presence of 37% formalin in refluxing ethanol for 5 h to give the corresponding chromone derivatives **9a,b** in high yields (70–80%). The resulting products represent an important class of chromone derivatives, in which two different fragments with remarkably interesting biological and pharmaceutical activities are linked at the same carbon atom.

In conclusion, we have shown that the reaction of 2-(polyfluoroalkyl)chroman-4-ones with isopropyl nitrite is a simple and practical method for the preparation of 3-hydroxy-2-(polyfluoroalkyl)chromones and 3-hydroxychromone. Treatment of 3-acetoxy-2-(trifluoromethyl)chromone with primary amines and hydrazine gave the corresponding ammonium salts. 3-Hydroxychromone reacts with formaldehyde and α-aminoacids to form previously unknown *N*-(3-hydroxychromone-2-ylmethyl)-α-aminoacids.

EXPERIMENTAL

^{1}H (400 MHz), ^{19}F (376 MHz), and ^{13}C (100 MHz) NMR spectra were recorded on a Bruker DRX-400 spectrometer in DMSO-d_6 and $CDCl_3$ with TMS and $CFCl_3$ as the internal standards. IR spectra were recorded on Perkin-Elmer Spectrum BX-II and Bruker Alpha instruments as KBr discs and ATR (ZnSe), respectively. Elemental analyses were performed at the Microanalysis Services of the Institute of Organic Synthesis, Ural Branch, Russian Academy of Sciences. Melting points are uncorrected. All solvents used were dried and distilled per standard procedures. The starting 2-(polyfluoroalkyl)chroman-4-ones **3a–c** were prepared according to described procedure [10].

General procedure for the synthesis of 3-hydroxy-2-(polyfluoroalkyl)chromones (4a–c). Concentrated hydrochloric acid (3.4 mL) was added dropwise over 1 h to a cold stirred solution of chroman-4-one **3** (2.0 mmol) and isopropyl nitrite (6.0 mmol) in ethanol (5 mL) and methanol (2 mL). On completion of the addition, the reaction mixture was allowed to warm to room temperature (1 h) and was then heated to 80°C for 2–3 h. After cooling, the precipitated product was isolated by filtration and washed with water to give colorless crystals.

3-Hydroxy-2-(trifluoromethyl)chromone (4a). Yield 290 mg (68%), mp 166–167°C; IR (ATR) 3275, 1634, 1612, 1576 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.53 (ddd, 1H, H-6, J = 8.0, 7.1, 1.0 Hz), 7.73 (dd, 1H, H-8, J = 8.6, 1.0 Hz), 7.88 (ddd, 1H, H-7, J = 8.6, 7.1, 1.7 Hz), 8.14 (dd, 1H, H-5, J = 8.0, 1.7 Hz), 10.71 (s, 1H, OH); ^{19}F NMR (376 MHz, DMSO-d_6) δ −64.90 (s, CF_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 118.48 (C8), 120.33 (q, CF_3, $^1J_{C,F}$ = 273.4 Hz), 121.48 (C4a), 125.16 (C5/6), 125.39 (C6/5), 133.71 (q, C2, $^2J_{C,F}$ = 36.5 Hz), 135.04 (C7), 141.29 (C3), 154.07 (C8a), 173.59 (C=O). Anal. Calcd. for $C_{10}H_5F_3O_3$: C, 52.19; H, 2.19. Found: C, 52.15; H, 2.39.

3-Hydroxy-2-(difluoromethyl)chromone (4b). Yield 180 mg (42%), mp 184–185°C; IR (KBr) 3265, 1633, 1609 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.33 (t, 1H, CF_2H, $^2J_{H,F}$ = 51.8 Hz), 7.51 (ddd, 1H, H-6, J = 8.0, 7.1, 1.0 Hz), 7.73 (dd, 1H, H-8, J = 8.6, 1.0 Hz), 7.86 (ddd, 1H, H-7, J = 8.6, 7.1, 1.7 Hz), 8.13 (dd, 1H, H-5, J = 8.0, 1.7 Hz), 10.38 (s, 1H, OH); ^{19}F NMR (376 MHz, DMSO-d_6) δ −122.80 (d, CF_2H, $^2J_{F,H}$ = 51.8 Hz). Anal. Calcd. for $C_{10}H_6F_2O_3$: C, 56.61; H, 2.85. Found: C, 56.72; H, 2.86.

3-Hydroxy-2-(1,1,2,2-tetrafluoroethyl)chromone (4c). Yield 470 mg (66%), mp 134–135°C; IR (KBr) 3238, 1628, 1611, 1575 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.96 (tt, 1H, CF_2CF_2H, $^2J_{H,F}$ = 51.9 Hz, $^3J_{H,F}$ = 5.5 Hz), 7.54 (ddd, 1H, H-6, J = 8.0, 7.1, 1.0 Hz), 7.71 (dd, 1H, H-8, J = 8.6, 1.0 Hz), 7.88 (ddd, 1H, H-7, J = 8.6, 7.1, 1.7 Hz), 8.14 (dd, 1H, H-5, J = 8.0, 1.7 Hz), 10.70 (s, 1H, OH). Anal. Calcd. for $C_{11}H_6F_4O_3$: C, 50.40; H, 2.31. Found: C, 50.66; H, 2.46.

3-Methoxy-2-(trifluoromethyl)chromone (5). To a solution of chromone **4a** (400 mg, 1.74 mmol) and MeI (740 mg, 5.22 mmol) in acetone (10 mL) was added K_2CO_3 (600 mg, 4.35 mmol) and the mixture was reflux for 8 h. After cooling, the inorganic salts were filtered off and washed with acetone (10 mL). Evaporation of the filtrate at heating gave a solid, which was recrystallized from hexane to give colorless crystals. Yield 370 mg (87%), mp 57°C; IR (ATR) 1614 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.04 (s, 3H, MeO), 7.46 (ddd, 1H, H-6, J = 8.1, 7.1, 1.0 Hz), 7.55 (dd, 1H, H-8, J = 8.6, 1.0 Hz), 7.75 (ddd, 1H, H-7, J = 8.6, 7.1, 1.7 Hz), 8.24 (dd, 1H, H-5, J = 8.1, 1.7 Hz). Anal. Calcd. for $C_{11}H_7F_3O_3$: C, 54.11; H, 2.89. Found: C, 54.03; H, 3.14.

3-Acetoxy-2-(trifluoromethyl)chromone (6). A solution of **6** (330 mg, 1.43 mmol) and acetic anhydride (300 mg, 2.87 mmol) in pyridine (5 mL) was kept at room temperature for 2 days. Then the reaction mixture was poured into diluted hydrochloric acid (1:10) and allowed to stand for 1 day at room temperature. The resulting colorless solid was filtered and washed with water. Yield 300 mg (77%), mp 110°C; IR (ATR) 1790, 1664, 1611 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.41 (s, 3H, Me), 7.64 (ddd, 1H, H-6, J = 8.0, 7.1, 1.0 Hz), 7.85 (ddd, 1H, H-8, J = 8.6, 1.0, 0.4 Hz), 7.98 (ddd, 1H, H-7, J = 8.6, 7.1, 1.7 Hz), 8.13 (ddd, 1H, H-5, J = 8.0, 1.7, 0.4 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −67.87 (s, CF_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.00 (Me), 118.44 (C8), 118.75 (q, CF_3, $^1J_{C,F}$ = 275.8 Hz), 123.56 (C4a), 126.27 (C5/6), 126.29 (C6/5), 135.18 (C7/3), 135.26 (C3/7), 144.80 (q, C2, $^2J_{C,F}$ = 37.7 Hz), 154.73 (C8a), 167.17 (OC=O), 171.73 (C=O). Anal. Calcd. for $C_{12}H_7F_3O_4$: C, 52.95; H, 2.59. Found: C, 52.99; H, 2.79.

General procedure for the synthesis of ammonium salts of 3-hydroxy-2-(trifluoromethyl)chromone (7a–d). To a solution of **6** (270 mg, 1.0 mmol) in absolute ethanol (5 mL) was added the corresponding amine (4.0 mmol). The resulting colorless solid was filtered, washed with cooled ethanol, and dried at 60–70°C.

Isoamylammonium 2-(trifluoromethyl)chromone-3-olate (7a). Yield 150 mg (47%), mp 132–133°C; IR (ATR) 3035, 2958, 2874, 1633, 1609, 1584, 1557 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.70 (d, 6H, 2Me, J = 6.6 Hz), 1.29–1.36 (m, 2H, CH_2), 1.48 (sept, 1H, CH, J = 6.6 Hz), 2.85–2.90 (m, 2H, NCH_2), 6.70 (br s, 3H, NH_3^+), 7.31 (ddd, 1H, H-6, J = 8.1, 7.0, 1.0 Hz), 7.46 (d, 1H, H-8, J = 8.6 Hz), 7.63 (ddd, 1H, H-7, J = 8.6, 7.0, 1.7 Hz), 8.17 (dd, 1H, H-5, J = 8.1, 1.7 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 22.60 (qm, 2 Me, $J_{C,H}$ = 125.0 Hz), 25.50 (dm, CH, $J_{C,H}$ = 127.0 Hz), 36.70 (tm, CH_2, $J_{C,H}$ = 127.0 Hz), 37.77 (tm, CH_2, $J_{C,H}$ = 140.0 Hz), 118.60 (dd, C8, $J_{C,H}$ = 165.4, 7.0 Hz), 121.99 (dd, C4a, $J_{C,H}$ = 7.7, 4.0 Hz), 123.40 (dd, C5/6, $J_{C,H}$ = 163.6, 7.3 Hz), 123.84 (q, CF_3, $^1J_{C,F}$ = 270.7 Hz), 125.75 (dd, C6/5, $J_{C,H}$ = 164.3, 8.0 Hz), 131.75 (q, C2, $^2J_{C,F}$ = 31.5 Hz), 133.10 (dd, C7, $J_{C,H}$ = 164.3, 8.8 Hz), 152.27 (br s, C3), 154.20 (t, C8a, $J_{C,H}$ = 8.8 Hz), 180.38

(s, C=O). Anal. Calcd. for $C_{15}H_{18}F_3NO_3$: C, 56.78; H, 5.72; N, 4.41. Found: C, 56.34; H, 5.38; N, 4.18.

Benzylammonium 2-(trifluoromethyl)chromone-3-olate (7b). Yield 250 mg (74%), mp 167–168°C; IR (ATR) 3167, 1597, 1547 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.93 (s, 2H, CH_2), 4.72 (br s, 3H, NH_3^+), 7.11 (tt, 1H, H-4', J = 7.3, 1.3 Hz), 7.18–7.22 (m, 2H, H-3', H-5'), 7.25–7.29 (m, 2H, H-2', H-6'), 7.40 (ddd, 1H, H-6, J = 8.1, 7.1, 1.0 Hz), 7.51 (ddd, 1H, H-8, J = 8.6, 1.0, 0.4 Hz), 7.72 (ddd, 1H, H-7, J = 8.6, 7.1, 1.7 Hz), 8.18 (ddd, 1H, H-5, J = 8.1, 1.7, 0.4 Hz). Anal. Calcd. for $C_{17}H_{14}F_3NO_3$: C, 60.54; H, 4.18; N, 4.15. Found: C, 60.47; H, 4.21; N, 4.23.

(4-Fluorobenzyl)ammonium 2-(trifluoromethyl)chromone-3-olate (7c). Yield 300 mg (85%), mp 156–157°C; IR (ATR) 2895, 1633, 1608, 1585, 1546, 1512 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.96 (br s, 3H, NH_3^+), 3.87 (s, 2H, CH_2), 6.96–7.02 (m, 2H, arom.), 7.26–7.30 (m, 2H, arom.), 7.47 (ddd, 1H, H-6, J = 8.1, 7.1, 1.0 Hz), 7.57 (dd, 1H, H-8, J = 8.6, 1.0 Hz), 7.78 (ddd, 1H, H-7, J = 8.6, 7.1, 1.7 Hz), 8.23 (dd, 1H, H-5, J = 8.1, 1.7 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −65.14 (s, CF_3), −115.23 (br s, F). Anal. Calcd. for $C_{17}H_{13}F_4NO_3$: C, 57.47; H, 3.69; N, 3.94. Found: C, 57.85; H, 3.49; N, 3.92.

Hydrazinium 2-(trifluoromethyl)chromone-3-olate (7d). Yield 180 mg (69%), mp 118–119°C; IR (ATR) 3320, 3243, 1630, 1610, 1594, 1550 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.20 (br s, 5H, $NH_2NH_3^+$), 7.34 (ddd, 1H, H-6, J = 8.0, 7.0, 1.0 Hz), 7.54 (d, 1H, H-8, J = 8.6 Hz), 7.69 (ddd, 1H, H-7, J = 8.6, 7.0, 1.7 Hz), 8.04 (dd, 1H, H-5, J = 8.0, 1.7 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 118.63 (C8), 121.94 (C4a), 123.58 (C5/6), 123.64 (q, CF_3, $^1J_{C,F}$ = 270.7 Hz), 125.74 (C6/5), 131.98 (q, C2, $^2J_{C,F}$ = 32.3 Hz), 133.28 (C7), 151.90 (br s, C3), 154.19 (C8a), 180.29 (C=O). Anal. Calcd. for $C_{10}H_9F_3N_2O_3 \cdot 0.5H_2O$: C, 44.29; H, 3.72; N, 10.33. Found: C, 44.63; H, 3.50; N, 10.20.

3-Hydroxychromone (8). This compound was prepared from chroman-4-one analogously to **4**. Yield 290 mg (35%), mp 178–180°C (lit. [17a] mp 179–180°C); ^1H NMR (400 MHz, DMSO-d_6) δ 7.46 (ddd, 1H, H-6, J = 8.0, 7.0, 1.0 Hz), 7.63 (dd, 1H, H-8, J = 8.5, 1.0 Hz), 7.77 (ddd, 1H, H-7, J = 8.5, 7.0, 1.7 Hz), 8.12 (dd, 1H, H-5, J = 8.0, 1.7 Hz), 8.24 (s, 1H, H-2), 9.15 (s, 1H, OH).

N-(3-hydroxychromone-2-ylmethyl)-N-methylglycine (9a). A solution of **8** (200 mg, 1.23 mmol), sarcosine (110 mg, 1.23 mmol) and formaldehyde as 37% formalin (500 mg, 6.15 mmol) in ethanol (5 mL) was refluxed for 5 h. The reaction mixture was refrigerated until a crystalline precipitate appeared. The colorless solid was filtered off and washed with ethanol. Yield 260 mg (80%), mp 274–275°C; IR (ATR): 3018, 1630, 1608, 1574 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 2.39 (s, 3H, Me), 3.34 (s, 2H, CH_2), 3.89 (s, 2H, CH_2), 7.44 (br t, 1H, H-6, J = 7.5 Hz), 7.61 (d, 1H, H-8, J = 8.5 Hz), 7.76 (ddd, 1H, H-7, J = 8.5, 7.2, 1.5 Hz), 8.09 (br d, 1H, H-5, J = 8.0 Hz), 8.5–12.0 (br s, 2H, 2OH). Anal. Calcd. for $C_{13}H_{13}NO_5$: C, 59.31; H, 4.98; N, 5.32. Found: C, 59.41; H, 4.93; N, 5.02.

N-(3-hydroxychromone-2-ylmethyl)valine (9b). This compound was prepared from **8** and valine analogously to **9a**. Yield 200 mg (70%), mp 126–127°C; IR (ATR): 3295, 1613 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 0.85 (d, 3H, Me, J = 6.8 Hz), 0.89 (d, 3H, Me, J = 6.8 Hz), 1.85–1.95 (m, 1H, CH), 3.00 (d, 1H, NCH, J = 5.1 Hz), 3.85 (AB-system, 2H, CH_2, J = 14.6 Hz), 7.44 (ddd, 1H, H-6, J = 8.0, 7.1, 1.0 Hz), 7.60 (d, 1H, H-8, J = 8.5 Hz), 7.75 (ddd, 1H, H-7, J = 8.5, 7.1, 1.7 Hz), 8.08 (dd, 1H, H-5, J = 8.0, 1.7 Hz), OH non observed. Anal. Calcd. for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.81. Found: C, 62.05; H, 5.74; N, 4.92.

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