Electrolytic Partial Fluorination of Organic Compounds. 55.[1] Highly Regio- and Stereoselective Anodic Monofluorination of 2,3-Dihydrochroman-4-one and Chromone Derivatives

Kamal M. Dawood[†,‡] and Toshio Fuchigami*[,†]

Department of Electronic Chemistry, Tokyo Institute of Technology, 4259 Nagatsuta, Midori-ku, Yokohama 226-8502, Japan, and Department of Chemistry, Faculty of Science, Cairo University, Giza, Egypt

fuchi@echem.titech.ac.jp

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Anodic monofluorination at the position α to the oxygen atom of the (*E*)-3-benzylidene-2,3-dihydrochroman-4-one derivatives was successfully carried out to provide the corresponding 2-fluorochromanones selectively. This is the first regioselective electrochemical fluorination of fused-type, oxygen-containing heterocyclic compounds. Anodic fluorination of a chromone derivative also gave a similar fluorinated chromanone stereoselectively.

Introduction

The chroman-4-one moiety is an integral part of many natural products.[2] Chroman-4-one derivatives have also drawn much attention due to their anti-human-immunodeficiency-virus (HIV-1),[3] that causes acquired immune deficiency syndrome, and broad pharmacological[4] activities. Moreover, the biological potency of fluorinated heterocycles has been widely documented.[5−95−9] Therefore, considerable efforts have been paid to explore new synthetic routes to fluorinated heterocycles. The advantageous electrochemical method has been profoundly proven to be more applicable than the conventional, hazardous chemical methods.[10−12]Recently, we developed the selective anodic fluorination of flavones[13] and arylthioethylenecarbonates[14] as examples of oxygen-containing heterocycles. Crown ethers were also anodically fluorinated; however, α,ω-difluoro products due to ring opening were formed.[15] On the other hand, furan, benzofuran,[16] and morpholines[17] were anodically fluorinated; however, their fluorinated products were either not isolable due to their instability or isolable in very poor yields with low selectivity.

These results prompted us to conduct, for the first time, a successful highly regioselective anodic direct fluorination at the position α to the ring oxygen atom of the biologically active chroman-4-one derivatives **2a**−**c**.[18]

Results and Discussion

Synthesis of Starting Chroman-4-one and Chromone Derivatives 2 and 3. When an equimolar amount of chroman-4-one (**1**) and the appropriate aromatic aldehyde were heated at 80−90 °C, in the presence of a catalytic amount of piperidine, the corresponding (*E*)-3-benzylidene-2,3-dihydrochroman-4-one derivatives **2a**−**c**[19] were obtained in good yields. However, heating of **1** with

* To whom correspondence should be addressed. Tel/Fax: +81-45-924-5406.
† Tokyo Institute of Technology.
‡ Cairo University.

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Scheme 1

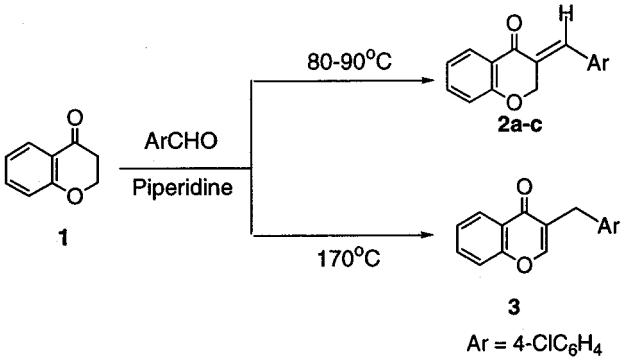
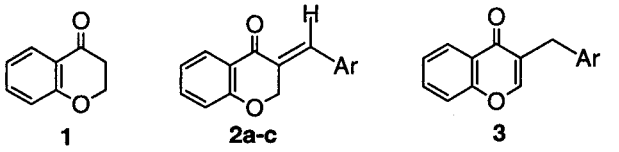


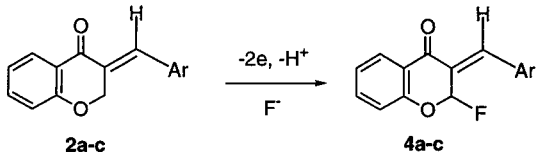
Table 1. Oxidation Potentials (E_p^{ox}) of Starting Substrates



compd. no.	Ar	E_p^{ox} (V vs SSCE)[a]
1		2.10
2a	C_6H_5	2.01
2b	4-ClC_6H_4	2.08
2c	4-BrC_6H_4	2.06
3	4-ClC_6H_4	2.17

[a] In 0.1 M $Bu_4N{\cdot}BF_4$/MeCN. Sweep rate: 100 mV s^{-1}.

Scheme 2



2,4; a: Ar = C_6H_5; **b**: Ar = 4-ClC_6H_4; **c**: Ar = 4-BrC_6H_4

4-chlorobenzaldehyde at 170 °C resulted in the direct formation of 3-(4-chlorobenzyl)chromone (**3**) in good yield as shown in Scheme 1.

Oxidation Potentials of Chroman-4-one and Chromone Derivatives. The oxidation peak potentials (E_p^{ox}) of chroman-4-one and chromone derivatives **1**, **2a**−**c**, and **3** were measured by cyclic voltammetry using a divided cell at a platinum anode in 0.1 M $Bu_4N{\cdot}BF_4$/anhydrous acetonitrile. These oxygen-containing heterocycles exhibited irreversible oxidation peaks, and all the values of E_p^{ox} are higher than 2 V versus the standard saturated calomel electrode (SSCE) as listed in Table 1. Interestingly, **2b** is more easily oxidized than **3**, and **2a**−**c** have lower oxidation potentials than **1**, which means that the electron transfer may take place from the olefin moiety rather than from oxygen.

Anodic Fluorination of Chroman-4-one Derivatives 2a−**c.** Constant current anodic oxidation of (*E*)-3-benzylidene-2,3-dihydrochroman-4-one (**2a**), as a model compound, was conducted using appropriate fluoride salts in dimethoxyethane (DME) and acetonitrile (MeCN). As shown in Scheme 2 and Table 2, highly regioselective anodic monofluorination proceeded, and only one fluorinated product was obtained regardless of the electrolytic conditions used. The fluorinated product was ascertained as (*E*)-3-benzylidene-2,3-dihydro-2-fluorochroman-4-one

Table 2. Anodic Fluorination of (*E*)-3-Benzylidene-2,3-dihydrochroman-4-ones (2a−c)

run	substrate	supporting electrolyte/solvent	charge passed (F/mol)	yield (%)[a]
1	**2a**	$Et_4NF{\cdot}4HF$/DME	6.5	72 (64)[b]
2	**2a**	$Et_4NF{\cdot}4HF$/DME[c]	5.5	17[d]
3	**2a**	$Et_4NF{\cdot}4HF$/MeCN	3.0	21[b]
4	**2a**	$Et_4NF{\cdot}4HF/CH_2Cl_2$	3.0	27[b]
5	**2a**	$Et_4NF{\cdot}4HF$ (neat)	6.0	0[e]
6	**2a**	$Et_4NF{\cdot}3HF$/DME	7.0	68[b]
7	**2a**	$Et_3N{\cdot}4HF$/DME	8.5	52[b]
8	**2a**	$Et_3N{\cdot}3HF$/DME	8.5	35[b]
9	**2b**	$Et_4NF{\cdot}4HF$/DME	7.0	60 (56)[b]
10	**2c**	$Et_4NF{\cdot}4HF$/DME	6.5	59 (58)[b]

[a] Calculated on the basis of ^{19}NMR, and the figures in parentheses are isolated yields. [b] A small amount of an unidentified product was formed. [c] An undivided cell was used. [d] A considerable amount of an unidentified, insoluble white polymeric product was formed. [e] The starting material **2a** was completely recovered.

(**4a**) on the basis of its elemental analysis and spectral data. Therefore, a fluorine atom attacks selectively the position α to the ring oxygen atom of **2a** to furnish **4a** in moderate to good yields. Among various electrolytic conditions, the use of $Et_4NF{\cdot}4HF$/DME in a divided cell (run 1) was the most effective for the formation of the fluorinated product **4a**.

An undivided cell was not suitable for the anodic synthesis of **4a** (run 2). In this case, the fluorination yield decreased drastically due to the formation of an undesirable, insoluble white polymeric product. Other electrolytic solvents such as acetonitrile (run 3) or hardly oxidizable dichloromethane (run 4) were also not effective, and the commonly reported acetamidation during fluorination of olefines[20,21] was not observed at all. Anodic fluorination did not proceed under neat conditions (run 5), and the starting material **2a** was completely recovered. When DME was used, a large excess amount of electricity was required due to the simultaneous oxidation of DME and **2**. Even when a large excess amount of electricity was passed, no difluorinated product was formed at all (runs 7 and 8). This can be explained as follows: DME has a higher ability to solvate the cationic part of fluoride salts to enhance the nucleophilicity of fluoride ions, and the overoxidation of the products is suppressed by the oxidation of DME itself during the electrolysis.[22−24] A possible mechanism for regioselective monofluorination of **2a** is depicted in Scheme 3. Initial electron transfer is assumed to take place at the olefin moiety of **2a** to give the radical cation **A** which undergoes deprotonation and further electron transfer to give the carbocation **B**. It was reported that isomerization occurs readily when the migrating double bond moves into conjugation with an aromatic benzene nucleus.[25] Therefore, it is conceivable that intermediate **B** isomerizes into **C**, followed by the predominant reaction of a fluoride ion with the cationic intermediate **C** to give **4a**. Benzylic nucleophilic substitution easily takes place; however, there was no evidence for the formation of the benzylic fluorinated product **5a**.

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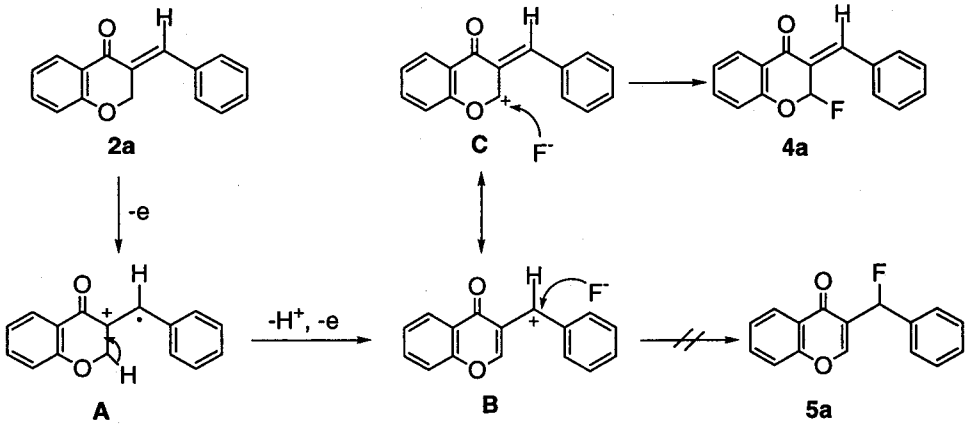
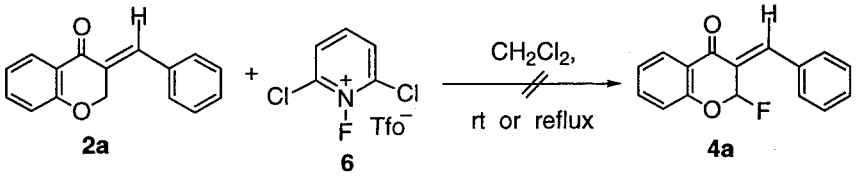
Scheme 3



Scheme 4



To generalize this interesting finding, we extended the anodic fluorination to other chroman-4-one derivatives **2b**,**c**, and similar results were obtained as shown in Table 2 (runs 9 and 10). In both cases, a fluorine atom was inserted regioselectively at the position α to the ring oxygen atom of **2b**,**c** to afford the corresponding 2-fluorochroman-4-ones **4b**,**c** in moderate yields as shown in Scheme 2.

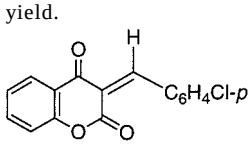
N-Fluoropyridinium salts are well known as powerful reagents for chemical fluorinations.[26,27] However, the reaction of *N*-fluoro-2,6-dichloropyridinium triflate (**6**) with the chromanone derivative **2a** in dichloromethane at either room temperature or refluxing conditions was unsuccessful, and **2a** was completely recovered (Scheme 4).

Anodic Fluorination of 3-(4-Chlorobenzyl)chromone (3). Furthermore, anodic fluorination of 3-(4-chlorobenzyl)chromone (**3**) was similarly attempted, and the results are outlined in Table 3. Interestingly, we found that the anodic fluorination of **3** offers stereoselective access to **4b** (Scheme 5). When $Et_4NF{\cdot}4HF$/DME and $Et_3N{\cdot}4HF$/DME in a divided cell were employed, **4b** was obtained in reasonable yield (runs 1 and 3). Since the oxidation potential of **3** is rather high (2.17 V vs SSCE), acetonitrile was expected to give much better results than DME; however, acetonitrile was not effective (run 2). In all cases, an appreciable amount of 3-(4-chlorobenzylidene)-1-benzopyran-2,4-dione (**7**) was isolated as a byproduct (cf. Experimental Section). Formation of **4b** from **3** is in sharp contrast to our previous report for the anodic fluorination of flavones.[13] In the case of flavones, 3-fluoroflavone and 2,3-difluoroflavanone derivatives were formed as shown in Scheme 6. In this work, the expected fluorinated products **8** and **9**, however, were not detected at all. Thus, anodic fluorination of chromanone **2b** and homoisoflavone **3** provided the same regioselectively

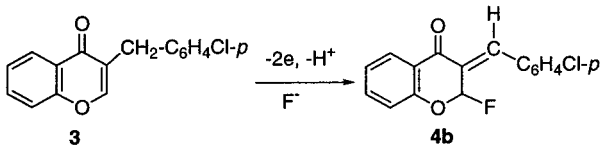
Table 3. Anodic Fluorination of 3-(4-Chlorobenzyl)chromone (3)

run	supporting electrolyte/ solvent	charge passed[a] (F/mol)	yield (%)[b,c]
1	$Et_4NF{\cdot}4HF$/DME	12	20
2	$Et_4NF{\cdot}4HF$/MeCN	4.5	6
3	$Et_3N{\cdot}4HF$/DME	10	18

[a] Constant current electrolysis (6 mA cm^{-2}) using a divided cell was applied. [b] Calculated on the basis of ^{19}F NMR. [c] 3-(4-Chlorobenzylidene)-1-benzopyran-2,4-dione (**7**) as a byproduct was isolated in 10−14% yield.



Scheme 5



monofluorinated product **4b** having the same stereoselectivity with respect to the olefin moiety. This result is quite interesting from the mechanistic point of view. A proposed mechanism for the anodic synthesis of **4b** from **3** is outlined in Scheme 7. A fluoride ion is assumed to attack the radical cation **D** to form **E**, which is further oxidized to give the fluorocarbocation **F**, followed by elimination of a proton from the benzylic methylene group of **F** to afford the thermodynamically more stable[28] 2-fluorochroman-4-one derivative **4b** rather than its isomer.[9] The *E* form of 3-benzylidene-2,3-dihydrochroman-4-one (**2a**) is normally predominant over its *Z* form.[29,30] For this reason, stereoselective synthesis of **4b** from **3** is consequently quite reasonable.

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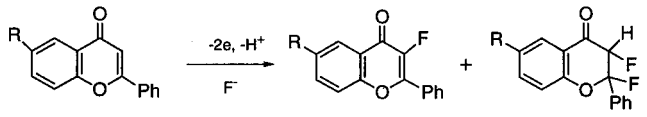
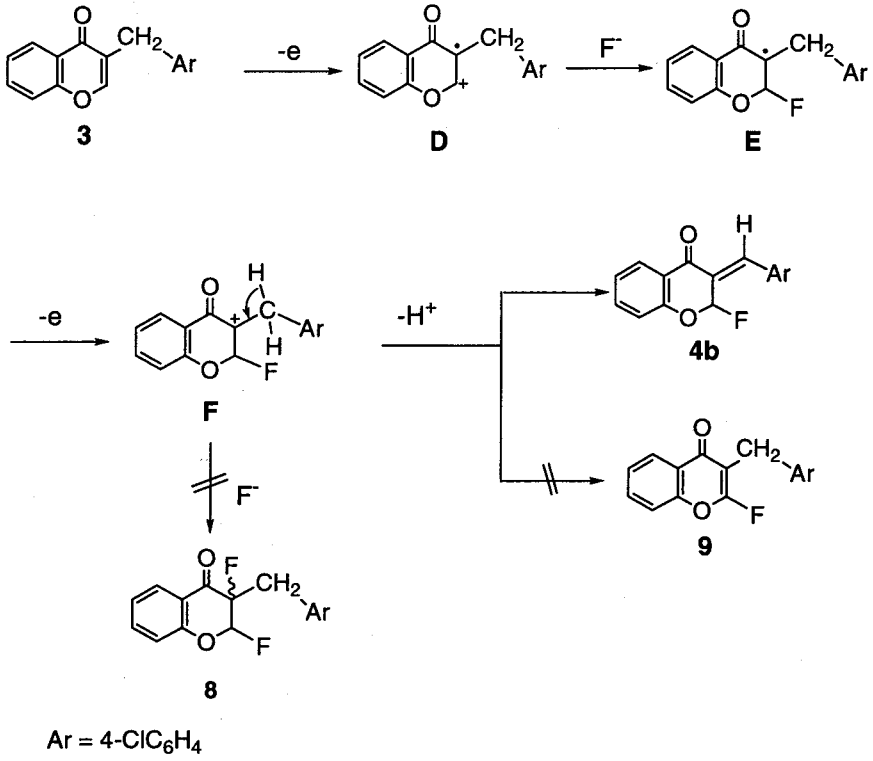
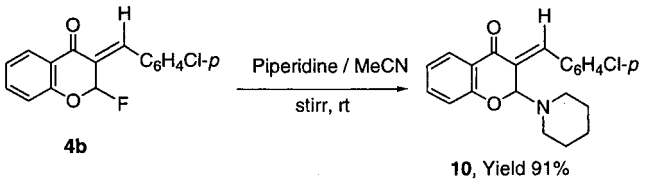
Scheme 6



Scheme 7



Scheme 8



Finally, the synthetic application of the 2-fluorochroman-4-one derivative **4b** was also attempted. Thus, treatment of **4b** with piperidine in acetonitrile at room temperature furnished the 2-piperidylchroman-4-one derivative **10** in an excellent yield as shown in Scheme 8.

Conclusions

In conclusion, we have developed two anodic stereoselective routes for direct fluorination at the position α to the ring oxygen atom of chroman-4-ones. This is the first report of successful regioselective electrochemical direct fluorination of fused-type, oxygen-containing heterocyclic compounds. The methodology seems to be of potential synthetic value.

Experimental Section

^{1}H NMR, ^{19}F NMR, and ^{13}C NMR spectra were recorded at 270, 254, and 68 MHz, respectively, in $CDCl_3$. The chemical shifts for ^{1}H NMR and ^{13}C NMR are given in δ ppm downfield from internal TMS, and the chemical shifts for ^{19}F NMR are given in δ ppm downfield from internal C_6F_6 [δ ($CFCl_3$) of the C_6F_6 reference is −162.2 ppm]. The 3-benzylidene-2,3-dihydrochroman-4-one **2a**−**c** derivatives were synthesized following the known reported procedure.[19]

Synthesis of 3-(4-Chlorobenzyl)chromone (3). To a mixture of 4-chromanone (**1**) (1.48 g, 10 mmol) and 4-chlorobenzaldehyde (1.4 g, 10 mmol) was added a catalytic amount of piperidine (0.5 mL). The reaction mixture was heated under reflux at 170 °C for 2 h and then cooled. The solid product was recrystallized from ethanol to give **3** in 1.59 g (59%) yield. mp 131−132 °C. ^{1}H NMR: δ 3.78 (s, 2H), 7.25−7.44 (m, 6H), 7.62 (m, 1H), 7.66 (s, 1H), 8.22 (d, 1H, J = 8.08 Hz). MS (*m*/*z*): 272 ($M^+ + 2$), 271 ($M^+ + 1$), 270 (M^+), 269 ($M^+ - 1$), 249, 207, 149, 134, 121, 105, 77. Anal. Calcd for $C_{16}H_{11}ClO_2$: C, 70.99; H, 4.10. Found: C, 71.19; H, 4.26.

Anodic Fluorination of Chroman-4-one and Chromone Derivatives. Constant current electrolysis (6 mA cm^{-2}) was conducted at a platinum anode and cathode (2 × 2 cm^2) in a solution of an appropriate fluoride salt (0.3 M) in dimethoxyethane (30 mL) to which chromanone **2** or chromone **3** derivative (1 mmol) was added. An H-type divided cell with a glass membrane under a nitrogen atmosphere at ambient temperature was used, and the electrolysis was carried out until the starting substrate was almost completely consumed. After the electrolysis was complete, the fluoride salts were removed by passing the resulting electrolytic solution through a short column on silica gel using ethyl acetate as an extracting eluent. The collected solution was evaporated under vacuum. The yield of the fluorinated product was then calculated on the basis of the ^{19}F NMR spectrum using a certain amount of monofluorobenzene as an internal standard, where the yield was calculated on the basis of the integral ratios between the monofluorobenzene and the resulted fluorinated product.

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Finally, the product was purified through long-column chromatography on silica gel using a hexane/ethyl acetate eluent mixture (5:1).

(*E*)-3-Benzylidene-2,3-dihydro-2-fluorochroman-4-one (4a). mp 69−70 °C. ^{1}H NMR: δ 6.76 (d, 1H, J = 45.20 Hz), 7.33−7.49 (m, 7H), 7.63 (dd, 1H, J = 8.58, 7.26 Hz), 7.96 (s, 1H), 8.17 (d, 1H, J = 7.92 Hz). ^{13}C NMR ($CDCl_3$): δ 87.75 (d, J = 173.3 Hz), 118.06, 123.77, 124.06, 125.33, 125.71, 126.19, 128.44, 128.68, 133.87, 137.48, 137.79, 153.53, 153.69, 156.15, 175.54. ^{19}F NMR: δ −101.40 (d, J = 45.04 Hz). MS (*m*/*z*): 254 (M^+), 234 (M^+ − HF), 205, 178, 133, 117, 92, 76. Anal. Calcd for $C_{16}H_{11}FO_2$: C, 75.58; H, 4.36. Found: C, 75.92; H, 4.55.

(*E*)-3-(4-Chlorobenzylidene)-2,3-dihydro-2-fluorochroman-4-one (4b). mp 93−94 °C. ^{1}H NMR ($CDCl_3$): δ 6.69 (d, 1H, J = 45.19 Hz), 7.29−7.42 (m, 6H), 7.62 (dd, 1H, J = 8.58, 6.93 Hz), 7.98 (s, 1H), 8.14 (d, 1H, J = 7.91 Hz). ^{13}C NMR ($CDCl_3$) (DEPT): δ 87.25 (d, J = 173.3 Hz), 118, 125.33, 125.53, 127.6, 127.7, 128.53, 133.89, 153.15, 153.33 (CH's), 123.29, 123.6, 134.44, 136.17, 156.04, 175.33 (C's). ^{19}F NMR: δ −102.50 (d, J = 45.04 Hz). MS (*m*/*z*): 290 (M^+ + 2), 289 (M^+ + 1), 288 (M^+), 268 (M^+ − HF), 233, 205, 176, 149, 121, 83. Anal. Calcd for $C_{16}H_{10}ClFO_2$: C, 66.56; H, 3.49. Found: C, 66.74; H, 3.77.

(*E*)-3-(4-Bromobenzylidene)-2,3-dihydro-2-fluorochroman-4-one (4c). mp 80−81 °C. ^{1}H NMR ($CDCl_3$): δ 6.69 (d, 1H, J = 45.19 Hz), 7.34−7.52 (m, 6H), 7.67 (dd, 1H, J = 7.91, 6.93 Hz), 7.99 (s, 1H), 8.17 (d, 1H, J = 7.92 Hz). ^{19}F NMR: δ −102.76 (d, J = 45.04 Hz). MS (*m*/*z*): 334 (M^+ + 2), 333 (M^+ + 1), 332 (M^+), 314, 313, 312, 233, 205, 176, 126, 92, 83. Anal. Calcd for $C_{16}H_{10}BrFO_2$: C, 57.68; H, 3.03. Found: C, 57.59; H, 3.25.

3-(4-Chlorobenzylidene)-1-benzopyran-2,4-dione (7). mp 162−163 °C (EtOH). ^{1}H NMR ($CDCl_3$): δ 7.42−7.57 (m, 4H), 7.73−7.81 (m, 3H), 8.25 (dd, 1H, J = 7.92, 1.65 Hz), 8.33 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 118.31, 124.76, 124.85, 126.21, 126.38, 128.68, 130.91, 134.50, 135.47, 139.87, 155.99, 159.06, 174.61, 190.73. MS (*m*/*z*): 286 (M^+ + 2), 285 (M^+ + 1), 284 (M^+), 254, 252, 234, 176. Anal. Calcd for $C_{16}H_9ClO_3$: C, 67.50; H, 3.19. Found: C, 67.58; H, 3.41.

3-(4-Chlorobenzylidene)-2-(1-piperidyl)-2,3-dihydrochroman-4-one (10). To a solution of the 2-fluorochroman-4-one derivative **4b** (0.144 g, 0.5 mmol) in acetonitrile (10 mL) was added piperidine (0.1 mL, 1 mmol). The reaction mixture was stirred at room temperature for 12 h. After the reaction was complete, the solvent was evaporated under vacuum, and the residue was passed through column chromatography using hexane/ethyl acetate (3:1) to afford 0.16 g (91%) of **10**. mp 59−60 °C. ^{1}H NMR: δ 1.46−1.58 (m, 6H), 2.36−2.43 (m, 4H), 4.74 (s, 1H), 7.23−7.44 (m, 7H), 7.60−7.66 (dd, 1H, J = 8.4, 7.1 Hz), 8.16 (s, 1H). ^{13}C NMR: δ 24.65, 26.32, 53.03, 64.49, 117.96, 124.96, 125.24, 125.86, 128.43, 129.53, 133.35, 139.70, 154.30, 155.97, 176.58. MS (*m*/*z*): 354 (M^+ + 1), 353 (M^+), 352, 311, 298, 269, 234, 177, 121, 84. Anal. Calcd for $C_{21}H_{20}ClNO_2$: C, 71.28; H, 5.70; N, 3.69. Found: C, 71.61; H, 5.98; N, 3.82.

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