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TRANSFORMATIONS OF 4-HYDROXY-5,6,7,8-TETRAFLUOROCOUMARIN DERIVATIVES WITH MONOAMINES

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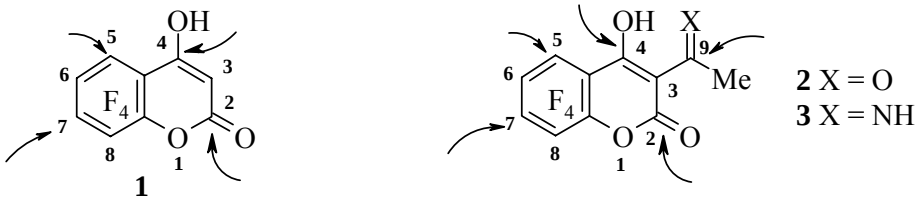
Abstract – The 4-hydroxy-5,6,7,8-tetrafluorocoumarin reacts with the monoamines to form salts under the mild conditions or the 4-alkyl(aryl)aminocoumarins on refluxing in *o*-xylene. The 3-acetyl-4-hydroxy-5,6,7,8-tetrafluorocoumarin reacts with the strong basic amines in the polar solvents to give salts that can be transformed into the 3-alkylaminoethylidene-5,6,7,8-tetrafluorobenzopyran-2,4-diones. The latter can be obtained by reaction of the 3-acetylcoumarin with different amines. The reactions of the 3-acetylcoumarin with the strong basic amines in dimethyl sulfoxide lead to the 7-alkylamino-3-alkylaminoethylidene-5,6,8-triflurobenzopyrandiones. The 3-acetimidoyl-4-hydroxy-5,6,7,8-tetrafluoro-coumarin affords the 3-alkylaminoethylidenebenzopyrandiones with the monoamines, but in dimethyl sulfoxide the 7-substituted 3-acetimidoyl-5,6,8-trifluorobenzopyrandiones or the 7-alkylamino-3-alkylaminoethylidene-5,6,8-triflurobenzopyrandiones can be obtained**.**

INTRODUCTION

The 4-hydroxycoumarin derivatives are widely used as luminescent markers, dyes, medicinal products and chemicals.[1] In this connection, the 4-hydroxycoumarins are the promising objects for their modification to search such compounds that could possess of the practically useful characteristics. We have developed the effective methods to obtaining the 4-hydroxy-5,6,7,8-tetrafluorocoumarin and the 3-substituted derivatives.[2] The reactions of the 3-substituted 4-hydroxy-5,6,7,8-tetrafluorocoumarins with ammonia and

morpholine in which the aromatic nucleophilic substitution of a fluorine at the C(7) position is the main process had been studied early.[3] However, the 4-hydroxy-5,6,7,8-tetrafluorocoumarin (**1**), the 3-acyl- (**2**) and the 3-acetimidoyl- (**3**) substituted derivatives are polyfunctional compounds having a few reaction centers. Nucleophilic attack is possible at the C(2) position of the coumarins (**1-3**) followed by opening of the α-pyron ring to give the 3-(3,4,5,6-tetrafluorophenyl-2-hydroxy)-3-oxoprop-2-enamide derivatives. The attack can proceed also at the C(7) or/and C(5) atoms of the aromatic nucleus with substitution of a fluorine to give the substituted coumarin derivatives. Amines can react with the coumarins (**1-3**) at the C(4) position with substitution of a hydroxyl group or forming salts. Besides, condensation at the acyl or acetimidoyl substituent (the C(9) centre) may occur in the case of the coumarins (**2,3**).



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Scheme 1

Non-fluorinated 4-hydroxycoumarin is known to react with monoamines at the C(4) to give 4-substitued coumarins or at the C(2) to form open-chain products.[4]

Herein, we report the reaction of the 4-hydroxy-5,6,7,8-tetrafluorocoumarins (**1-3**) with the various primary amines having different basicity to show the real reactivity of these compounds.

RESULTS AND DISCUSSION

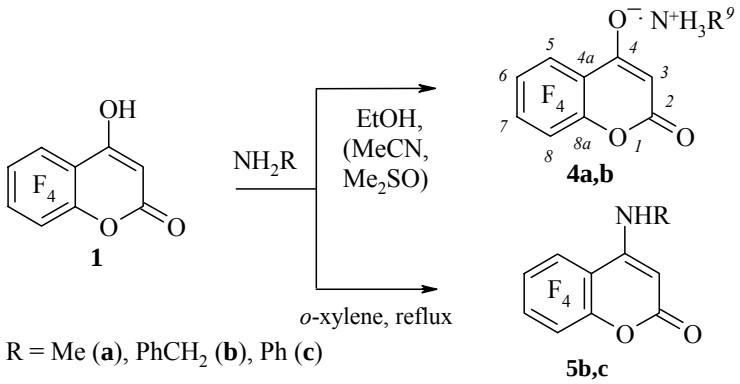
2.1. Reactions of the 4-hydroxy-5,6,7,8-tetrafluorocoumarin with amines.

We have studied the reaction of the 4-hydroxycoumarin (**1**) with the primary amines such as methylamine, benzylamine and aniline.

It has been found that the coumarin (**1**) reacts with the strong-basic amines (methylamine and benzylamine) at room temperature to afford compounds (**4a,b**) regardless of a solvent (acetonitrile, ethanol, dimethyl sulfoxide) (Scheme 2). In contrast, aniline does not react with coumarin (**1**) in such reaction conditions. According to the elemental analysis, IR, ^{1}H and ^{13}C NMR data, compounds (**4a,b**) have structure of salts. The IR spectra of compounds (**4a**,**b**) have the high-frequency absorption bands that are typical for the C=O stretching vibrations in the lactone fragment of the coumarins. In the ^{1}H NMR spectra of compounds (**4a,b**) the most characteristic signals are the one proton singlet of the methine groups and the three proton widened singlet of the amino groups. The ^{13}C NMR spectra have two low field signals corresponding to the C(2) and C(4) atoms of salts (**4a,b**) (see experimental part).

The compounds (**4a**,**b**) are stable under the mild conditions. Attempts to subject the products (**4a**,**b**) to further transformations were failed. So refluxing the products (**4a**,**b**) in toluene gives a mixture of

products that is difficult to separate.



Scheme 2

The formation of the stable salts (**4a**,**b**) in the reactions of the coumarin (**1**) with methylamine and benzylamine in contrast to the analogous transformation with aniline can explain by the higher basicity of methylamine (pK_b = 2.34) and benzylamine (pK_b = 4.67) in comparison with aniline (pK_b = 9.37).[5]

Under the drastic conditions (refluxing in *o*-xylene) the coumarin (**1**) condenses with benzylamine and aniline at the C(4) centre to give the 4-amino substituted coumarins (**5b**,**c**) (Scheme 2) similarly to the non-fluorinated 4-hydroxycoumarin.[5]

2.2. Reactions of the 3-acetyl-4-hydroxy-5,6,7,8-tetrafluorocoumarin with monoamines.

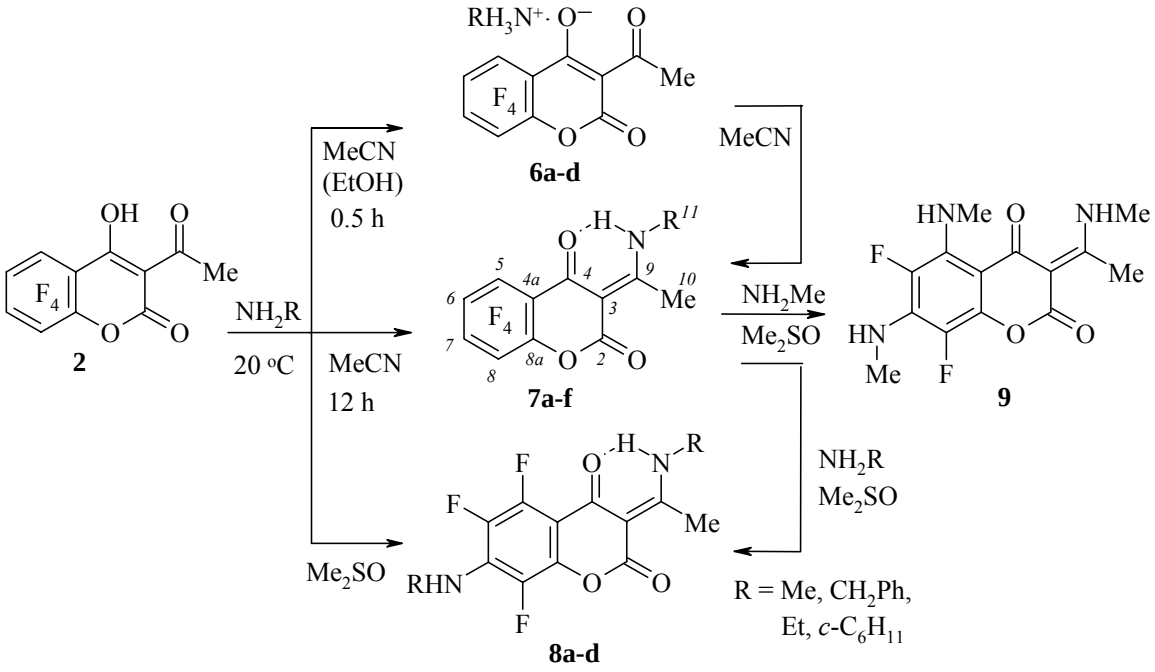
The reaction of the 3-acetyl-4-hydroxycoumarin (**2**) with the primary amines (methylamine, cyclohexylamine, ethylamine, benzylamine, *p*-anisidine and aniline) was found to depend on solvent used (scheme 3). Thus, the coumarin (**2**) reacts with the strong-basic amines (methylamine, cyclohexylamine (pK_b = 3.34)[5], ethylamine (pK_b = 3.92)[5] and benzylamine) in acetonitrile and ethanol at room temperature to give salts (**6a-d**) similarly to transformations of the 4-hydroxycoumarin (**1**). The IR spectra of the products (**6a-d**) are characterized by the presence of the high-frequency absorption bands corresponding to the lactone fragment. In the ^{1}H NMR spectra of the compounds (**6a-d**), the signals of salts are observable. It is interesting that the mass spectrum of the product (**6a**) does not contain the molecular ion peak, and the fragmentation characteristic of this product and its highest peak correspond to the initial coumarin (**2**).

In contrast to the products (**4a**,**b**), the compounds (**6a-d**) are unstable, and they are transformed easily into the 3-alkylaminoethylidenebenzopyran-2,4-diones (**7a-d**) on standing in acetonitrile at room temperature for 12 h (scheme 3). The benzopyrandiones (**7a-d**) can be directly obtained by reaction of the coumarin (**2**) with amines in acetonitrile for 12 h as a result of the condensation at the acetyl substituent. In a similar manner the coumarin (**2**) reacts with the aromatic amines (aniline and *p*-anisidine) to produce the benzopyrandiones (**7e,f**).

Reactions of the coumarin (**2**) with the strong basic amines (methylamine, ethylamine, cyclohexylamine

and benzylamine) in dimethyl sulfoxide lead to the 7-alkylaminosubstituted 3-alkylaminoethylidenebenzopyrandiones (**8a-d**) (Scheme 3) if even the excess of amine does not used. In these case, the amine condensation at the acetyl group of the coumarin (**2**) is accompanied by the substitution of a fluorine atom at the C(7) position by the second molecule of amine. The 7-alkylaminosubstituted heterocycles (**8a-d**) can be obtained by reactions of the benzopyrandiones (**7a-d**) with corresponding amines in dimethyl sulfoxide also.

Similar reactions of the coumarin (**2**) with aniline and *p*-anisidine in dimethyl sulfoxide furnish the benzopyrandiones (**7e,f**) only.

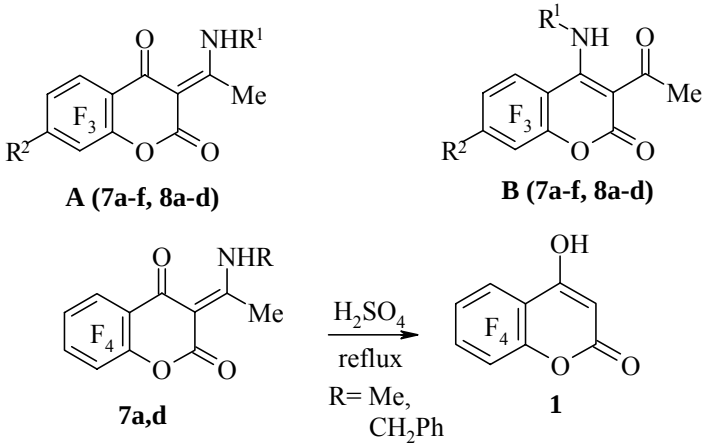


R = Me (**6a, 7a, 8a**), *c*-C_6H_{11} (**6b, 7b, 8b**), Et (**6c, 7c, 8c**), $PhCH_2$ (**6d, 7d, 8d**), C_6H_4OMe-4 (**7e**), Ph (**7f**)

Scheme 3

All attempts to subject the coumarin (**2**) to ring opening of the heterocycle failed. Prolonged treatment of the benzopyrandione (**7a**) with methylamine (as the strongest basic amine) furnishes the 5,7-disubstituted benzopyrandiones (**9**) only (Scheme 3). The formation of the product (**9**) is accompanied by the considerable resinification of the reaction mixture.

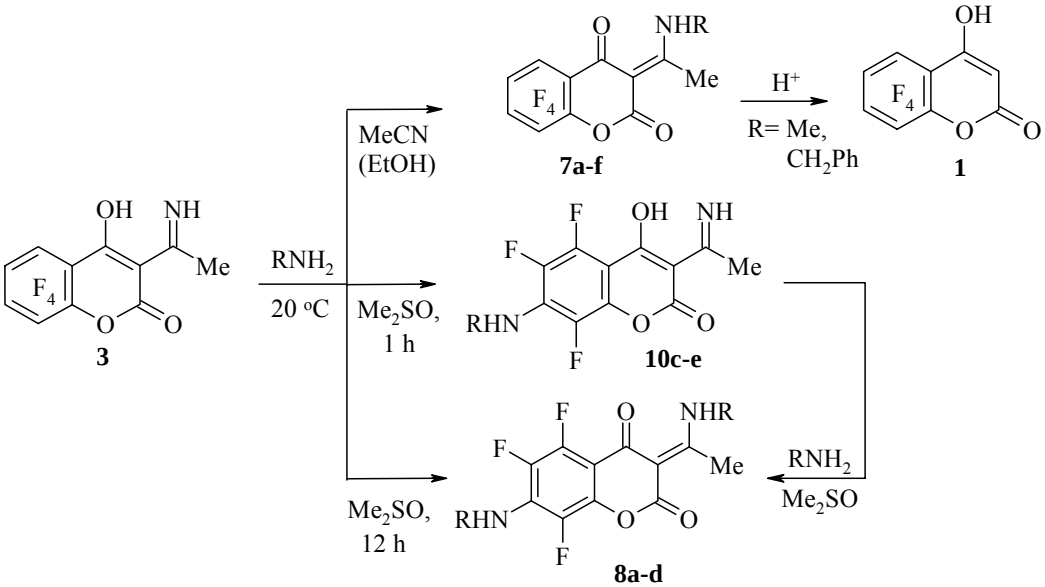
In principle, one has to consider two isomeric structures for condensation products (**7**) and (**8**), namely 3-alkylaminoethylidenebenzopyran-2,4-diones (**A**) or the isomeric 3-acetyl-4-alkylaminocoumarins (**B**) (Scheme 4). However, we assign the structure of 3-alkylaminoethylidenebenzopyran-2,4-diones of type (**A**) to these products using the chemical method. So, the compounds (**7a,d**) were treated with concentrated H_2SO_4 to give 4-hydroxy-5,6,7,8-tetrafluorocoumarine (**1**) (Scheme 4) that is possible in the case of benzopyrandiones (**A**) only.



Scheme 4

2.3. Reactions of the 3-acetimidoyl-4-hydroxy-5,6,7,8-tetrafluorocoumarin with the monoamines.

The reactions of the 3-acetimidoyl-4-hydroxycoumarin (**3**) with the same monoamines in different solvents have been studied. It was found that the 3-acetimidoylcoumarin (**3**) does not form salts in acetonitrile or ethanol in contrast to the 3-acetylcoumarin (**2**), and the benzopyrandiones (**7a-f**) are the main products in these solvents (Scheme 5). The formation of the compounds (**7a-f**) proceeds due to the reamination of the amino group at the acetimidoyl substituent (the centre C(9)) by the nucleophilic molecule.



R = Me (**7a**, **8a**), *c*-C_6H_{11} (**7b, 8b**), Et (**8c, 10c**), $PhCH_2$ (**7d**, **8d**, **10d**), C_6H_4OMe-4 (**7e, 10e**), Ph (**7f**)

Scheme 5

When dimethyl sulfoxide was used as a solvent, the reactions of the coumarin (**3**) with the equimolar quantity of amines (ethylamine, benzylamine, *p*-anisidine) having medium basicity result in the formation of the 7-substituted benzopyran-2,4-diones (**10c-e**). In the case of the strong basic amines such as methylamine and hexylamine, the benzopyrandiones (**8a,b**) are isolated as the main products (Scheme 5).

The benzopyrandiones (**8c,d**) can be obtained from coumarin (**3**) when excess of the corresponding amine is employed.

Obviously, the first reaction step of the coumarin (**3**) with amines in dimethyl sulfoxide is the attack of the nucleophiles at the C(7) center. The formation of the 7-monosubstituted heterocycles (**10c-e**) in the reaction of the coumarin (**3**) with such amines as ethylamine, benzylamine, *p*-anisidine confirms this supposition.

CONCLUSION

In the present work we have shown that the reactions of the 5,6,7,8-tetrafluoro-4-hydroxycoumarins (**1-3**) proceed ambiguously depending on the reaction conditions and the initial substrates structure. In contrast to the similar transformations with the non-fluorinated 4-hydroxycoumarins[4], the α-pyron ring of the fluorinated coumarins (**1-3**) is stable and does not subject to opening in the reactions with the monoamines. The specific feature of the fluorinated 4-hydroxycoumarins (**1**, **2**) is their ability to form the stable salts with the strongly basic amines. Acidity of the hydroxyl group is increased due to the presence of the electron-withdrawing fluorine atoms in the aromatic ring that activate the neighbouring hydroxyl group. In the case of the 3-acetimidoyl-4-hydroxycoumarin (**3**) the salt formation does not occur. Probably, the hydroxyl group deacidification determines by the presence of the adjacent acetimidoyl substituent.

Besides, the reactions of the nucleophilic aromatic substitution of the fluorine atoms are peculiar to the coumarins (**2, 3**) in the interactions with the highly basic amines in polar solvents. Probably, the presence of the electron-withdrawing substituent at the C(3) position of the coumarins (**2, 3**) promotes to the substitution of the fluorine atoms.

EXPERIMENTAL

The melting points were measured in open capillaries and are uncorrected. The infrared spectra were recorded on Perkin Elmer Spectrum One FT-IR spectrometer at 4000 – 400 cm^{-1} in the nujol mulls. The ^{1}H and ^{13}C NMR spectra were measured on Bruker DRX-400 spectrometer (^{1}H, 400, ^{13}C, 100.6 MHz) relative to Me_4Si. The ^{19}F NMR spectra were obtained on a Bruker DRX-400 spectrometer (^{19}F, 376 MHz) using C_6F_6 as the internal standard. The mass spectra were recorded on Varian MAT-311A instrument. The microanalyses were carried out on Perkin-Elmer PE 2400 series II elemental analyzer.

The starting coumarins (**1-3**) were obtained by the methods.[2]

4.1. The general procedures of the reactions of the coumarins (**1-3**) with amines

Method *A*. An amine (0.1 mmol) was added to a solution of the coumarin (**1**) (0.1 mmol) in *o*-xylene (50 mL). The reaction mixture was refluxed for 18 h. The solvent was removed and the residue was recrystallized from the corresponding solvent.

Method *B*. An excess of the gaseous methylamine was bubbled through a solution of coumarin (0.1 mmol) in an appropriate solvent (20 mL) at 20 °C for 0.5 h to obtaining the salts (**4a**), for 12 h to obtaining (**7a**, **8a**) and for 24 h to obtaining (**9**). The reaction control was monitored by TLC method. The solvent was removed and the residue was recrystallized from the corresponding solvent.

Method *C*. An amine (0.1 mmol) was added to a solution of coumarin (0.1 mmol) in an appropriate solvent (20 mL) at 20 °C. The mixture was stirred for 0.5 h to obtaining the salts (**4a,b**, **6b-d**) and for 12 h to obtaining benzopyrandiones (**7b-f, 8b-d, 10c-e**). The solvent was removed and the residue was recrystallized from the corresponding solvent.

Method *D*. An amine (0.25 mmol) was added to a solution of the coumarin (**3**) (0.1 mmol) in Me_2SO (20 mL) at 20 °C. The mixture was stirred for 12 h to obtaining benzopyrandiones (**8c,d**). The solvent was removed and the residue was recrystallized from the corresponding solvent.

4.2.1. Methylammonium 5,6,7,8-tetrafluoro-2-oxo-4-benzo-*2H*-pyranolate (**4a**).

Compound (**4a**) was obtained from coumarin (**1**) according to method *B*. Yield after recrystallization from chloroform, 78 % (20.69 mg) in DMSO, 81 % (21.48 mg) in MeCN, 84 % (22.28 mg) in EtOH; mp 172-173 °C. ^{1}H NMR (DMSO-d_6) δ: 2.41 (3H, s, Me), 4.49 (1H, s, CH), 7.66 (3H, s, NH_3^+). ^{13}C NMR [$(CD_3)_2SO$] δ: 24.48 (*s*, C-9), 85.06 (*s*, C-3), 109.90 (*m*, C-4a), 133.79-136.41 (*dm*, $^2J_{C\text{-}F}$= 244.7 Hz, C-6, C-7), 139.81 (*m*, C-8a), 142.72-145.36 (d*m*, $^2J_{C\text{-}F}$= 255.8 Hz, C-5, C-8), 161.97 (*m*, C-4), 172.20 (m, C-2). ^{19}F NMR (DMSO-d_6) δ: -5.15 (1F, m), 1.22 (1F, m), 5.99 (1F, m), 15.32 (1F, m). IR, ν: 3205, 3061, 2769, 2583, 1614 (NH^+), 1708 (OC=O), 1654 (C=C), 1554, 1520 (C=C), 1021 (CF). Anal. Calcd for $C_{10}H_7NO_3F_4$: C 45.30; H 2.66; F 28.66; N 5.28. Found: C 45.27; H 2.59; F 28.90; N 5.51.

4.2.2. Benzylammonium 5,6,7,8-tetrafluoro-2-oxo-4-benzo-*2H*-pyranolate (**4b**).

Compound (**4b**) was obtained from coumarin (**1**) and benzylamine according to method *C*. Yield after recrystallization from hexane, 69 % (23.55 mg) in DMSO, 85 % (29.01 mg) in MeCN, 84 % (28.67 mg) in EtOH; mp 169-170 °C. ^{1}H NMR (DMSO-d_6) δ: 4.05 (2H, s, CH_2); 4.43 (1H, s, CH); 7.37-7.47 (5H, m, Ph); 8.14 (3H, s, NH_3^+). ^{13}C NMR (DMSO-d_6) δ: 42.38 (*s*, C-9); 85.03 (*s*, C-3); 110.01 (*m*, C-4a); 128.44 (*s*, C-*o*); 128.60 (*s*, C-*p*); 128.80 (*s*, C-*m*); 134.06 (*s*, C-*i*); 133.66-136.40 (*dm*, $^2J_{C\text{-}F}$ = 244.5 Hz, C-6, C-7); 139.84 (*m*, C-8a); 142.69-145.42 (d*m*, $^2J_{C\text{-}F}$ = 255.5 Hz, C-6, C-7); 161.99 (*d*, C-4); 172.21 (*m*, C-2). ^{19}F NMR (DMSO-d_6) δ: -5.87 (1F, m); 0.94 (1F, m); 4.98 (1F, m), 13.96 (1F, m). IR, ν: 3425, 3003, 2654 (NH_3^+); 1673 (OC=O); 1648 (C=C); 1577, 1523 (NH_3^+, C=C); 1028 (CF). Anal. Calcd for $C_{16}H_{11}NO_3F_4$: C 56.31; H 3.25; F 22.27; N 4.10. Found: C 55.95; H 3.03; F 21.92; N 3.76.

4.1.1. 4-Benzylamino-5,6,7,8-tetrafluorocoumarin (**5b**).

Compound (**5b**) was obtained from coumarin (**1**) and benzylamine according to method *A*. Yield after recrystallization from EtOH, 73 % (23.59 mg); mp 220-223 °C. ^{1}H NMR (DMSO-d_6) δ: 4.27 (2H, *d*,

NHCH$_2$Ph, $^3J_{H\text{-}H}$ = 5.9 Hz); 5.41 (1H, s, =CH); 7.22-7.32 (5H, m, Ph); 8.67 (1H, m, NH). ^{19}F NMR (DMSO-*d*$_6$) δ: -0.98 (1F, m); 4.41 (1F, m); 11.55 (1F, m); 19.28 (1F, m). IR, ν: 3374 (NH); 1693 (OC=O); 1576, 1544, 1520 (C=C); 1014 (C-F). Anal. Calcd for $C_{16}H_9NO_2F_4$: C 59.45; H 2.81; F 23.51; N 4.33. Found: C 59.12; H 2.99; F 23.13; N 4.25.

4.1.2. 4-Anilino-5,6,7,8-tetrafluorocoumarin (**5c**).

Compound (**5c**) was obtained from coumarin (**1**) and aniline according to method *A*. Yield after recrystallization from EtOH, 79 % (24.43 mg); mp 245-250 °C. ^{1}H NMR (DMSO-*d*$_6$) *δ*: 5.15 (1H, s, CH); 7.34-7.54 (5H, m, C_6H_5); 8.98 (1H, s, NH). ^{19}F NMR (DMSO-*d*$_6$) δ: -1.55 (1F, m); 3.38 (1F, m); 10.79 (1F, m); 21.58 (1F, m). IR, ν: 3341, 1658 (N-H); 1700 (OC=O); 1571, 1514, 1463 (C=C); 1017, 1003 (C-F). Anal. Calcd for $C_{15}H_7NO_2F_4$: C, 58.26; H, 2.28; F, 24.58; N, 4.53. Found: C, 58.26; H, 2.16; F, 24.47; N, 4.40.

4.1.3. Methylammonium 3-acetyl-5,6,7,8-tetrafluoro-2-oxo-4-benzo-*2H*-pyranolate (**6a**).

Compound (**6a**) was obtained from coumarin (**2**) according to method *B*. Yield after recrystallization from hexane, 62 % (19.05 mg) in MeCN, 65 % (19.97 mg) in EtOH; mp 175-176 °C. ^{1}H NMR (DMSO-*d*$_6$) *δ*: 2.31 (3H, s, Me), 2.40 (3H, s, Me), 7.61 (3H, s, NH_3^+). ^{19}F NMR (DMSO-*d*$_6$) δ: -5.61 (1F, m), 0.52 (1F, m), 6.91 (1F, m), 14.62 (1F, m). IR, ν: 3200, 2870, 1629 (NH), 1715 (OC=O), 1650 (C=O), 1566, 1520, 1510 (C=C), 1028 (C-F). EIMS, 70 eV, *m/z* (rel. int): 276 $[M - NH_2Me]^+$ (64), 261 $[M - NH_2Me - Me]^+$ (23), 234 $[M - NH_2Me - COMe]^+$ (49), 193 $[HOC_6F_4C{=}O]^+$ (41), 192 $[OC_6F_4C{=}O]^+$ (100), 164 $[C_6F_4O]^+$ (17), 136 $[C_5F_4]^+$ (14), 117 $[C_5F_3]^+$ (10), 69 $[HOC{=}C\text{-}C{=}O]^+$ (24). Anal. Calcd for $C_{12}H_9NO_4F_4$: C 46.92; H 2.95; F 24.74; N 4.56. Found: C 47.16; H 2.99; F 24.87; N 4.41.

4.1.4. Cyclohexylammonium 3-acetyl-5,6,7,8-tetrafluoro-2-oxo-4-benzo-*2H*-pyranolate (**6b**).

Compound (**6b**) was obtained from coumarin (**2**) and cyclohexylamine in EtOH according to method *C*. Yield after recrystallization from EtOH, 83 % (31.15 mg); mp 171-174 °C. ^{1}H NMR (DMSO-*d*$_6$) *δ*: 1.39-1.88 (10H, m, $(CH_2)_5$); 2.48 (3H, s, Me); 4.10 (1H, s, HC); 7.33 (3H, s, NH_3^+). ^{19}F NMR (DMSO-*d*$_6$) *δ*: -2.35 (1F, m); 1.95 (1F, m); 11.88 (1F, m); 16.76 (1F, m). IR, ν: 3003 (NH_3^+); 1703 (OC=O); 1645 (C=O); 1534, 1507, 1479 (NH_3^+, C=C); 1019 (C-F). Anal. Calcd for $C_{17}H_{17}NO_4F_4$: C 46.53; H 3.90; F 17.32; N 3.19. Found: C 47.05; H 3.09; F 17.58; N 3.14.

4.1.5. Ethylammonium 3-acetyl-5,6,7,8-tetrafluoro-2-oxo-4-benzo-*2H*-pyranolate (**6c**).

Compound (**6c**) was obtained from coumarin (**2**) and ethylamine in EtOH according to method *C*. Yield after recrystallization from EtOH, 78 % (25.05 mg); mp 168-171 °C. ^{1}H NMR (DMSO-*d*$_6$) *δ*: 1.28 (3H, *t*, $NHCH_2\underline{Me}$, $^3J_{H\text{-}H}$= 7.2 Hz); 2.37 (3H, *s*, Me); 3.68 (2H, q, $NH\underline{CH_2}Me$, $^3J_{H\text{-}H}$= 7.2 Hz); 7.45 (3H, s, NH_3). ^{19}F NMR (DMSO-*d*$_6$) *δ*: -2.74 (1F, m); 1.90 (1F, m); 11.71 (1F, m); 16.95 (1F, m). IR, ν: 2985 (NH_3^+);

1708 (OC=O); 1641 (C=O); 1548, 1521, 1499 (NH_3^+, C=C); 1027 (C-F). Anal. Calcd for $C_{13}H_{11}NO_4F_4$: C 40.58; H 2.88; F 19.75; N 3.64. Found: C 40.15; H 3.15; F 19.92; N 3.28.

4.1.6. Benzylammonium 3-acetyl-5,6,7,8-tetrafluoro-2-oxo-4-benzo-*2H*-pyranolate (**6d**).

Compound (**6d**) was obtained from coumarin (**2**) and benzylamine in EtOH according to method *C*. Yield after recrystallization from EtOH, 80 % (30.66 mg); mp 175-176 °C. ^{1}H NMR (DMSO-d_6) δ: 2.30 (3H, s, Me); 4.05 (2H, s, CH_2Ph); 7.36-7.47 (5H, m, Ph); 8.17 (3H, s, NH_3). ^{19}F NMR (DMSO-d_6) δ: -2.67 (1F, m); 1.97 (1F, m); 11.91 (1F, m); 16.99 (1F, m). IR, ν: 2972 (NH_3^+); 1704 (OC=O); 1643 (C=O); 1538, 1519, 1498 (NH_3^+, C=C); 1034 (C-F). Anal. Calcd for $C_{18}H_{13}NO_4F_4$: C 56.40; H 3.42; F 19.46; N 3.14. Found: C 55.92; H 3.09; F 19.46; N 3.14.

4.1.7. 3-(1-Methylaminoethyliden)-5,6,7,8-tetrafluoro-*2H,4H*-benzopyran-2,4-dione (**7a**).

a Compound (**7a**) was obtained from coumarin (**2**) in MeCN according to method *B*. Yield after recrystallization from EtOH, 80 % (23.14 mg); mp 174-175 °C. ^{1}H NMR (DMSO-d_6) δ: 2.61 (3H, s, Me), 3.23 (3H, d, NH<u>Me</u>, $^3J_{H\text{-}H}$= 5.0 Hz), 13.40 (1H, s, NH). ^{13}C NMR (DMSO-d_6) δ: 18.47 (*s*, C-10), 31.24 (*s*, C-11), 95.67 (*s*, C-3), 107.22 (*m*, C-4a), 133.62-136.28 (*dm*, $^2J_{C\text{-}F}$ = 248.4 Hz, C-6, C-7), 138.34 (*m*, C-8a), 143.48-146.27 (*dm*, $^2J_{C\text{-}F}$ = 261.4 Hz, C-5, C-8), 159.48 (*m*, $^4J_{C\text{-}F8}$= 1.0 Hz, C-2,), 176.5 (m, C-4), 176.90 (m, C-9). ^{19}F NMR (DMSO-d_6) δ: -2.82 (1F, m), 1.89 (1F, m), 11.51 (1F, m), 16.74 (1F, m). IR, ν: 3194, 1594 (NH), 1710 (OC=O), 1654 (C=O), 1617, 1531, 1491 (C=C), 987 (C-F). EIMS, 70 eV, *m/z* (rel. int): 289 $[M]^+$ (100), 274 $[M\text{-}Me]^+$ (42), 272 $[M\text{-}OH]^+$ (22), 97 $[HOC{=}C\text{-}C(=NMe)Me]^+$ (20), 82 $[HOC{=}C\text{-}C(=N)Me]^+$ (20), 69 $[HOC{=}C\text{-}C{=}O]^+$ (30), 56 $[C(=NMe)Me]^+$ (76). Anal. Calcd for $C_{12}H_7NO_3F_4$: C 49.84; H 2.44; F 26.28; N 4.84. Found: C 49.63; H 2.62; F 26.51; N 4.65.

b from coumarin (**3**) according to method *B*. Yield after recrystallization from EtOH, 79 % in MeCN, 75 % (21.69 mg) in EtOH; mp 174-175 °C.

c from salt (**6a**) (21.5 mg, 0.07 mmol) under stirring in MeCN (10 mL) for 12 h at 20 °C. Yield after recrystallization from EtOH, 95 % (19.23 mg); mp 174-175 °C.

4.1.8. 3-(1-Cyclohexylaminoethyliden)-5,6,7,8-tetrafluoro-*2H,4H*-benzopyran-2,4-dione (**7b**).

a Compound (**7b**) was obtained from coumarin (**2**) and cyclohexylamine in MeCN according to method *C*. Yield after recrystallization from EtOH, 78 % (27.87 mg); mp 172-174 °C. ^{1}H NMR (DMSO-d_6) δ: 1.32-1.95 (10H, m, $(CH_2)_5$); 2.65 (3H, s, Me); 4.02 (1H, s, CH); 13.56 (1H, m, NH). ^{19}F NMR (DMSO-d_6) δ: -2.74 (м, 1F); 1.92 (м, 1F); 11.77 (м, 1F); 17.11 (м, 1F). IR, ν: 1733 (OC=O), 1651 (C=O), 1595, 1522, 1498 (C=C), 1035, 975 (C-F). Anal. Calcd for $C_{17}H_{15}NO_3F_4$: C 57.15; H 4.23; F 21.27; N 3.92. Found: C 56.92; H 4.09; F 21.56; N 3.96.

b from coumarin (**3**) and cyclohexylamine in MeCN according to method *C*. Yield after recrystallization from EtOH, 75 % (26.80 mg); mp 172-174 °C.

c from salt (**6b**) (26.3 mg, 0.07 mmol) under stirring in MeCN (10 mL) for 12 h at 20 °C. Yield after recrystallization from EtOH, 96 % (25.01 mg); mp 173-174 °C.

4.1.9. 3-(1-Ethylaminoethyliden)-5,6,7,8-tetrafluoro-*2H,4H*-benzopyran-2,4-dione (**7c**).

a Compound (**7c**) was obtained from coumarin (**2**) and ethylamine in MeCN according to method *C*. Yield after recrystallization from EtOH, 80 % (24.26 mg); mp 160-161 °C. ^{1}H NMR (DMSO-d_6) δ: 1.22 (3H, t, NHCH$_2$Me, $^3J_{H\text{-}H}$= 7.2 Hz); 2.62 (3H, s, Me); 3.62-3.69 (2H, m, NHCH$_2$Me); 13.24 (1H, s, NH). ^{19}F NMR (DMSO-d_6) δ: -2.79 (м, 1F); 1.90 (м, 1F); 11.63 (м, 1F); 16.88 (м, 1F). Anal. Calcd for $C_{13}H_9NO_3F_4$: C 51.50; H 2.99; F 25.06; N 4.62. Found: C 52.42; H 2.87; F 24.78; N 4.56.

b from coumarin (**3**) and ethylamine in MeCN according to method *C*. Yield after recrystallization from EtOH, 75 % (22.74 mg); mp 160-161 °C.

c from salt (**6c**) (19.3 mg, 0.06 mmol) under stirring in MeCN (10 mL) for 12 h at 20 °C. Yield after recrystallization from ethanol, 88 % (16.01 mg); mp 160-161 °C.

4.1.10. 3-(1-Benzylaminoethyliden)-5,6,7,8-tetrafluoro-*2H,4H*-benzopyran-2,4-dione (**7d**).

a Compound (**7d**) was obtained from coumarin (**2**) and benzylamine in MeCN according to method *C*. Yield after recrystallization from EtOH, 88 % (31.09 mg); mp 140-142 °C.[2]

b from coumarin (**3**) and benzylamine according to method *C.* Yield after recrystallization from ethanol, 83 % (29.32 mg) in MeCN, 84 % (29.68 mg) in EtOH; mp 140-142 °C.

c from salt (**6d**) (26.8 g, 0.07 mmol) under stirring in MeCN (10 mL) for 12 h at 20 °C. Yield after recrystallization from EtOH, 92 % (22.75 mg); mp 140-142 °C.

4.1.11. 3-(1-(4-Methoxy)phenylaminoethyliden)-5,6,7,8-tetrafluoro-*2H,4H*-benzopyran-2,4-dione (**7e**).

a Compound (**7e**) was obtained from coumarin (**2**) and *p*-anisidine according to method *C*. Yield after recrystallization from EtOH, 76 % (28.98 mg) in DMSO, 92 % (35.08 mg) in MeCN, 85 % (32.41 mg) in EtOH; mp 174-175 °C. ^{1}H NMR (DMSO-d_6) δ: 2.56 (3H, s, Me); 3.82 (3H, s, OMe); 7.07-7.39 (4H, m, C_6H_4); 14.85 (1H, s, NH). ^{19}F NMR (DMSO-d_6) δ: -2.36 (1F, m); 2.23 (1F, m); 12.57 (1F, m); 17.48 (1F, m). IR, ν: 1715 (OC=O); 1651 (C=O), 1634, 1607, 1574 (C=C, C=N); 1011 (C-F). Anal. Calcd for $C_{18}H_{11}NO_4F_4$: C, 56.70; H, 2.91; F, 19.93; N, 3.67. Found: C, 56.24; H, 2.98; F, 20.15; N, 3.58.

b from coumarin (**3**) and *p*-anisidine in MeCN according to method *C*. Yield after recrystallization from EtOH, 87 % (33.17 mg); mp 174-175 °C.

4.1.12. 3-(1-Anilinoethyliden)-5,6,7,8-tetrafluoro-*2H,4H*-benzopyran-2,4-dione (**7f**).

a Compound (**7f**) was obtained from coumarin (**2**) and aniline according to method *C*. Yield after recrystallization from *n*-hexane, 68 % (23.89 mg) in DMSO, 83 % (29.16 mg) in MeCN, 80 % (28.10 mg) in EtOH; mp 165-167 °C. ^{1}H NMR (DMSO-d_6) δ: 2.58 (3H, s, Me); 7.44-7.58 (5H, m, Ph); 15.00 (1H, s, NH). ^{19}F NMR (DMSO-d_6) δ: -2.30 (1F, m); 2.27 (1F, m); 12.75 (1F, m); 17.57 (1F, m). IR, ν:

1718 (OC=O); 1653 (C=O), 1635, 1599, 1580 (C=C, C=N); 1010, 998 (C-F). Anal. Calcd for $C_{17}H_9NO_3F_4$: C, 58.13; H, 2.58; F, 21.63; N, 3.99. Found: C, 58.13; H, 2.46; F, 21.49; N, 3.79.

b from coumarin (**3**) and aniline according to method *C*. Yield after recrystallization from *n*-hexane, 72 % (25.29 mg) in DMSO, 84 % (29.51 mg) in MeCN, 83 % (29.16 mg) in EtOH; mp 165-167 °C.

4.1.13. 7-Methylamino-3-(1-methylaminoethyliden)-5,6,8-trifluoro-*2H,4H*-benzopyran-2,4-dione (**8a**).

a Compound (**8a**) was obtained from coumarin (**2**) in DMSO according to method *B*. Yield after recrystallization from *n*-hexane, 78 % (23.42 mg); mp 238-239 °C. ^{1}H NMR (DMSO-d_6) δ: 2.57 (3H, s, Me), 3.02 (3H, dt, C-7-NHMe, $^3J_{H\text{-}H}$ = 4.1, $^5J_{H\text{-}F}$ = 3.0 Hz), 3.17 (3H, d, NHMe, $^3J_{H\text{-}H}$ = 5.1 Hz), 6.57 (1H, m, C-7-NH), 13.24 (1H, s, NH). ^{19}F NMR (DMSO-d_6) δ: -1.20 (1F, m,), 2.04 (1F, m), 15.33 (1F, m). IR, ν: 3434, 3404, 3318, 1582 (NH), 1711 (OC=O), 1647 (C=N), 1607, 1549, 1504 (C=C), 1019 (CF). Anal. Calcd for $C_{13}H_{11}N_2O_3F_3$: C 52.01; H 3.69; F 18.98; N 9.33. Found: C 51.96; H 3.62; F 19.06; N 9.37.

b from coumarin (**3**) in DMSO according to method *B*. Yield after recrystallization from *n*-hexane, 82 % (24.62 mg); mp 238-239 °C.

c from benzopyran-2,4-dione (**7a**) in DMSO according to method *B*. Yield after recrystallization from *n*-hexane, 76 % (22.82 mg); mp 238-239 °C.

4.1.14. 7-Cyclohexylamino-3-(1-cyclohexylaminoethyliden)-5,6,8-trifluoro-*2H,4H*-benzopyran-2,4-dione (**8b**).

a Compound (**8b**) was obtained from coumarin (**2**) and cyclohexylamine in DMSO according to method *C*. Yield after recrystallization from *n*-hexane, 44 % (19.21 mg); mp 174-175 °C. ^{1}H NMR (DMSO-d_6) δ: 1.25-1.91 (20H, m, 2$(CH_2)_5$); 2.55 (3H, s, Me); 3.57 (1H, s, CH); 3.94 (1H, s, CH); 6.08 (1H, m, NH); 13.78 (1H, m, NH). ^{19}F NMR (DMSO-d_6) δ: 0.87 (1F, m); 3.68 (1F, m); 14.56 (1F, m). IR, ν: 3399 (N-H); 1698 (OC=O); 1648 (C=O), 1609, 1588 (C=C, C=N); 998 (C-F). Anal. Calcd for $C_{23}H_{27}N_2O_3F_3$: C, 63.29; H, 6.24; F, 13.06; N, 6.42. Found: C, 63.89; H, 6.23; F, 12.95; N, 6.55.

b from coumarin (**3**) and cyclohexylamine in Me_2SO according to method *C*. Yield after recrystallization from *n*-hexane, 45 % (19.64 mg); mp 174-175 °C.

4.1.15. 7-Ethylamino-3-(1-ethylaminoethyliden)-5,6,8-trifluoro-*2H,4H*-benzopyran-2,4-dione (**8c**).

a Compound (**8c**) was obtained from coumarin (**2**) and ethylamine in DMSO according to method *C*. Yield after recrystallization from EtOH, 38 % (12.48 mg); mp 183-186 °C. ^{1}H NMR (DMSO-d_6) δ: 1.16 (3H, t, $NHCH_2Me$, $^3J_{H\text{-}H}$ = 7.4 Hz); 1.28 (3H, t, $NHCH_2Me$, $^3J_{H\text{-}H}$ = 7.1 Hz); 2.64 (3H, s, Me); 3.25 (2H, q, CH_2Me, $^3J_{H\text{-}H}$ = 7.1 Hz); 3.64-3.69 (2H, m, $NHCH_2Me$); 9.65 (1H, s, NH); 13.28 (1H, s, NH). ^{19}F NMR (DMSO-d_6) δ: -0.58 (1F, m); 2.43 (1F, m); 14.57 (1F, m). IR, ν: 3389 (N-H); 1705 (OC=O); 1644 (C=O), 1612, 1564 (C=C, C=N); 1016 (C-F). Anal. Calcd for $C_{15}H_{15}N_2O_3F_3$: C, 45.98; H, 3.86; F, 14.55; N, 7.15. Found: C, 45.05; H, 3.86; F, 15.07; N, 7.32.

b from coumarin **3** and ethylamine in DMSO according to method *D*. Yield after recrystallization from

EtOH, 75 % (24.62 mg); mp 183-186 °C.

c from coumarin **10c** and ethylamine according to method *C*. Yield after recrystallization from EtOH, 65 % (21.34 mg) in DMSO; mp 183-186 °C.

4.1.16. 7-Benzylamino-3-(1-benzylaminoethyliden)-5,6,8-trifluoro-*2H,4H*-benzopyran-2,4-dione (**8d**).

a Compound (**8d**) was obtained from coumarin (**2**) and benzylamine in DMSO according to method *C*. Yield after recrystallization from EtOH, 70 % (31.67 mg); mp 175-176 °C. ^{1}H NMR (DMSO-d_6) δ: 2.70 (3H, s, Me); 4.55 (1H, s, NH); 4.67 (2H, d, NHCH$_2$Ph, $^3J_{H\text{-}H}$ = 6.1 Hz); 4.71 (2H, d, NHCH$_2$Ph, $^3J_{H\text{-}H}$ = 5.7 Hz); 7.26-7.41 (10H, m, 2Ph); 14.36 (1H, s, NH). ^{19}F NMR (DMSO-d_6) δ: -0.13 (1F, m); 3.66-3.70 (1F, m); 14.45 (1F, m). IR, ν: 3330 (NH); 1699 (OC=O); 1641 (C=O); 1574, 1518 (C=C); 1015 (CF). EIMS, 70 eV, *m/z* (rel. int): 452 $[C_{25}H_{19}F_3N_2O_3]^+$ (30), 361 $[M\text{-}CH_2Ph]^+$ (12), 106 $[NHCH_2Ph]^+$ (11), 91 $[CH_2Ph]$ (100). Anal. Calcd for $C_{25}H_{19}N_2O_3F_3$: C 66.37; H 4.23; F 12.60; N 6.19. Found: C 66.00; H 4.03; F 12.76; N 6.18.

b from coumarin (**3**) and benzylamine in DMSO according to method *D*. Yield after recrystallization from EtOH, 72 % (32.57 mg); mp 175-176 °C.

c from coumarin (**7d**) and benzylamine in Me_2SO according to method *C*. Yield after recrystallization from EtOH, 86 % (38.91 mg); mp 175-176 °C.

d from coumarin (**10d**) and benzylamine in Me_2SO according to method *C*. Yield after recrystallization from ethanol, 78 % (35.29 mg); mp 175-176 °C.

4.1.17. 6,8-Difluoro-5,7-dimethylamino-3-(1-methylaminoethyliden)-*2H,4H*-benzopyran-2,4-dione (**9**).

Compound (**9**) was obtained from benzopyrandione (**7a**) in DMSO according to method *B***.** Yield after column chromatography (with chloroform-acetone solution as an eluent in 10:1 ratio), 43 % (13.39 mg); mp 234-237 °C. ^{1}H NMR (DMSO-d_6) δ: 2.58 (3H, s, C-10-Me), 2.96 (3H, dd, C-5-NHMe, $^3J_{H\text{-}H}$ = 5.5, $^5J_{H\text{-}F}$ = 6.9 Hz), 2.58 (3H, m, C-7- NHMe), 3.15 (3H, d, C-9-NHMe, $^3J_{H\text{-}H}$ = 5.1 Hz), 6.05 (1H, s, NH), 8.56 (1H, s, NH), 12.89 (1H, s, NH). ^{19}F NMR (DMSO-d_6) δ: -7.70 (1F, m), 3.36 (1F, m). IR, ν: 3328, 3226, 1586 (NH), 1687 (OC=O), 1644 (C=O), 1600 (C=C), 1541, 1515 (C=C), 960 (CF). Anal. Calcd for $C_{14}H_{15}N_3O_3F_2$: C 54.02; H 4.86; F 12.21; N 13.50. Found: C 55.57; H 4.98; F 13.24; N 12.15.

4.1.18. 3-Acetimidoyl-7-ethylamino-5,6,8-trifluorocoumarin (**10c**)

Compound (**10c**) was obtained from coumarin (**3**) and ethylamine in DMSO according to method *C*. Yield after recrystallization from *n*-hexane, 88 % (26.42 mg); mp 149-151 °C. ^{1}H NMR (DMSO-d_6) δ: 1.17 (3H, t, CH$_2$Me, $^3J_{H\text{-}H}$ = 6.1 Hz); 3.41 (2H, m, CH$_2$Me); 6.54 (1H, s, NH); 9.97 (1H, s, NH); 11.86 (1H, s, OH). ^{19}F NMR (DMSO-d_6) δ: -0.72 (1F, m); 2.21 (1F, m); 13.97 (1F, m). IR, ν: 3520, 3331 (NH); 1712 (OC=O); 1648, 1525 (C=C, C=N); 1006 (C-F).Anal. Calcd for $C_{13}H_{11}N_2O_3F_3$: C 52.01; H 3.69; F 18.98; N 9.33. Found: C 53.41; H 3.09; F 19.01; N 9.17.

4.1.19. 3-Acetimidoyl-7-benzylamino-5,6,8-trifluorocoumarin (**10d**)

Compound (**10d**) was obtained from coumarin (**3**) and benzylamine in DMSO according to method *C*. Yield after recrystallization from *n*-hexane, 65 % (23.55 mg); mp 190-191 °C. ^{1}H NMR (DMSO-d_6) δ: 2.50 (3H, s, Me), 4.56 (2H, d, NH$\underline{CH_2}$Ph, $^3J_{H\text{-}H}$ = 6.7 Hz), 7.21-7.35 (5H, m, Ph), 6.03 (1H, s, NH); 9.87 (1H, s, NH), 11.83 (1H, s, OH). ^{19}F NMR (DMSO-d_6) δ: -0.46 (1F, m), 3.77 (1F, m), 14.05 (1F, m). IR, ν: 3541, 3318 (NH); 1710 (OC=O); 1648, 1551 (C=C, C=N); 998 (C-F).Anal. Calcd for $C_{18}H_{13}N_2O_3F_3$: C, 59.67; H, 3.62; F, 15.73; N, 7.73. Found: C, 60.15; H, 3.42; F, 14.99; N, 7.72.

4.1.20. 3-Acetimidoyl-7-(4-methoxy)phenylamino-5,6,8-trifluorocoumarin (**10e**)

Compound (**10e**) was obtained from coumarin (**3**) and *p*-anisidine in DMSO according to method *B*. Yield after recrystallization from EtOH, 70 % (26.48 mg); mp >210 °C. ^{1}H NMR (DMSO-d_6) δ: 2.50 (3H, s, Me); 3.73 (3H, s, OMe); 6.85-6.99 (4H, m, C_6H_4); 8.60 (1H, s, NH); 9.97 (1H, s, NH); 11.85 (1H, s, OH). ^{19}F NMR (DMSO-d_6) δ: 8.15 (1F, m); 12.78 (1F, m); 14.65 (1F, m). IR, ν: 3549, 3448, 3334 (NH); 1708 (OC=O); 1643, 1582, 1547 (C=C, C=N); 996 (C-F). Anal. Calcd for $C_{18}H_{13}N_2O_4F_3$: C 57.15; H 3.46; F 15.07; N 7.40. Found: C 57.69; H 3.33; F 15.65; N 7.21.

4.2. Hydrolysis of benzopyran-2,4-diones (**7a,d**).

A mixture of compound (**7a,d**) (1.0 mmol) and concentrated H_2SO_4 (1 ml) was heated at 100°C for 4 h. To the mixture, 10 ml of water was added. The resulting precipitate was collected by filtration, washed with water, dried and recrystallized from toluene to give 1.86 g (70% from (**7a**)) and 1.73 g (65% from (**7d**)) of coumarin (**1**); mp 222-225 °C (subl.).[2]

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