Synthesis and transformation of 6-aminomethyl derivatives of 7-hydroxy-2′-fluoroisoflavones

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Mannich aminomethylation of 8-methyl-7-hydroxy-2'-fluoroisoflavones applying bis-(*N,N*-dimethylamino)methane afforded C-6 substituted *N,N*-dimethylaminomethyl derivatives. Subsequent acetylation of these compounds in acetic anhydride in the presence of potassium acetate provided access to the corresponding acetoxymethyl derivatives that were converted to hydroxymethyl- and alkoxymethyl-substituted 7-hydroxyisoflavonoids. Addition of 3-(*N,N*-dimethylamino)-5,5-dimethyl-2-cyclohexen-1-one or 1,3-dimethyl-5-aminopyrazole with thermally generated *ortho*-quinone methides led to *hetero*-Diels–Alder or Michael adducts.

Introduction

It is widely known that the introduction of fluorine and fluorine-containing substituents into an organic molecule can significantly change the biological activity of the obtained compounds [1]. Since many of natural compounds are attractive for the development of new drugs [2], and chromones were recognized as a valid scaffold in medicinal chemistry [3], developing of new isoflavone derivatives for potential biologically active compounds is of current interest. Moreover, the introduction of fluorine-containing groups into ring B of isoflavones is also of undoubted interest. Thus, it was shown that A- or B-ring fluorinated isoflavones exhibit

diverse biological activity, and can be useful in the search process of new drugs. [4-10]. Among the reactions of isoflavone derivatives that lead to skeleton modification, the well-known tendency of phenolic substrates to enter Mannich condensation by interactions with formaldehyde and amines should be mentioned. This method is promising for the modification of previously derived isoflavonoid derivatives. Thus, it was shown that the interaction of 4'-fluoro-7-hydroxyisoflavones with primary aliphatic amines and formaldehyde in the presence of a catalytic amount of DMAP produces 3-(4-fluorophenyl)-9,10-dihydro-4*H*,8*H*-chromeno derivatives[8,7-*e*][1,3]oxazin-4-one [11]. Such

reactions are characteristic for 5-hydroxychromones, 7-hydroxychromones and 8-hydroxychromones. Thus, aminomethylation of 5,7-dihydroxychromones usually gave mixtures of 6- and 8-aminomethyl derivatives, where, in some cases, 6-aminomethyl derivatives were the major products, unless the formation of 8 substituted regioisomers was observed [12]. It was reported that such transformations may be regiospecific and regioselective. For instance, regiospecific Mannich aminomethylation of 7-hydroxyisoflavonoids using bis-(*N,N*-dimethylamino)methane afforded C-8 substituted *N,N*-dimethylaminomethyl adducts, while the regioselective aminomethylation of 5-hydroxy-7-methoxyisoflavonoids afforded predominant *N,N*-dimethylaminomethyl adducts [13]. In this work methods for obtaining 6-aminomethyl derivatives of 7-hydroxy-2′-fluoroisoflavones were developed, and their subsequent transformations were designed for the synthesis of isoflavones with biologically attractable substituents.
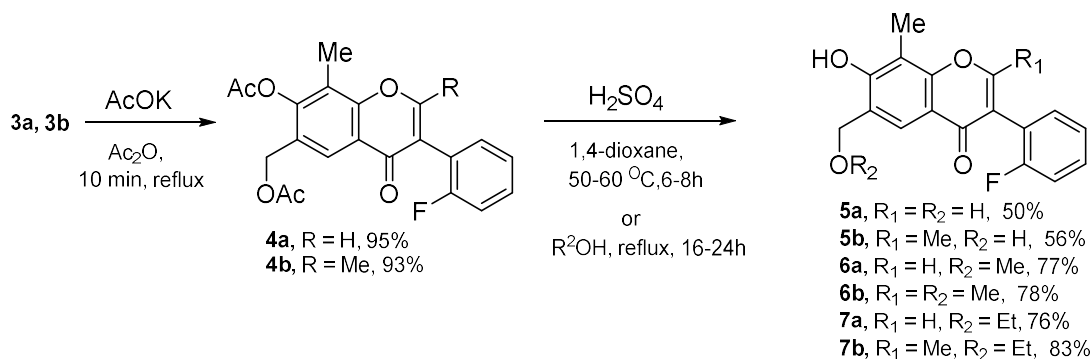
Results and discussion

The main strategy for the construction of isoflavones includes synthesis of hydroxylated diaryl ethanones (using Houben-Hoesch reaction [14] or Friedel-Crafts acylation of phenols [15]) with subsequent ring-closure reaction. The starting compound for the synthesis of B-ring fluorinated isoflavones deoxybenzoin **1** was prepared by reacting 2-methylresorcinol with (2-fluorophenyl)acetonitrile in boron trifluoride etherate medium with gaseous HCl, followed by treatment with water. Then, **1** was subjected to an intramolecular cyclization reaction in the presence of phosphorous oxytrichloride in solution of *N,N*-dimethylformamide or *N,N*-dimethylacetamide yielded 7-hydroxyisoflavones **2a** and **2b.** Subsequent aminomethylation reaction of compounds **2** with the twofold excess of bis-(*N,N*-dimethylamino)methane in 1,4-dioxane at reflux affords in the 6-(dimethylamino)methyl derivatives **3a** and **3b** (Scheme 1).
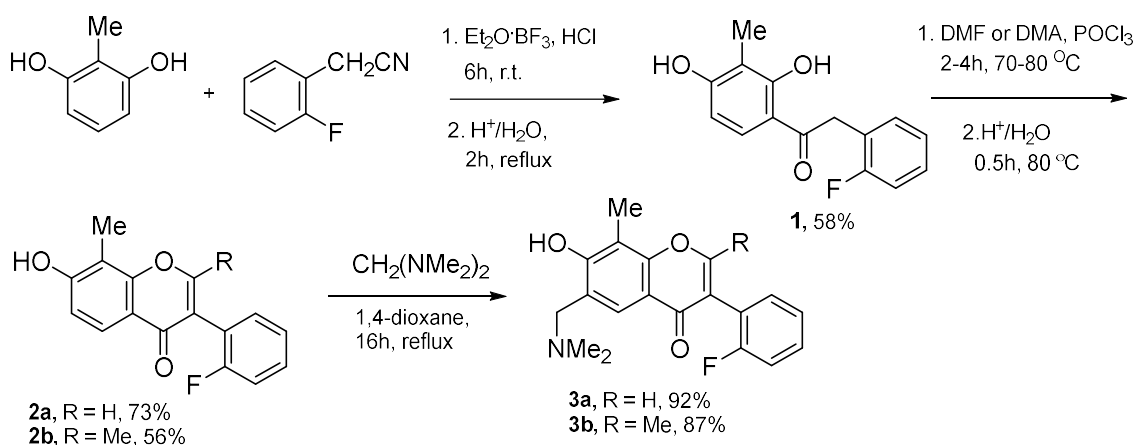
Scheme 1. Synthesis of 2'-fluoroisoflavones and their 6-aminomethyl derivatives.

The direct conversion of *N,N*-dimethylaminomethyl derivatives **3** into the corresponding diacetoxy derivatives **4** easily proceeded with good yields in acetic anhydride with presence of potassium acetate. Hydrolysis of such diacetates **4** in dioxane in the presence of 0.2 M aqueous sulfuric acid under moderate heating resulted in 7-hydroxy-6-hydroxymethyl derivatives **5a** and **5b** (Scheme 2). In case of using of methanol or ethanol as solvent for the deacetylation, the formation of 7-hydroxy-6-akkoxymethyl isoflavones **6** or **7** was observed.

5a, $R_1 = R_2 = H$, 50%
5b, $R_1 = Me$, $R_2 = H$, 56%
6a, $R_1 = H$, $R_2 = Me$, 77%
6b, $R_1 = R_2 = Me$, 78%
7a, $R_1 = H$, $R_2 = Et$, 76%
7b, $R_1 = Me$, $R_2 = Et$, 83%

4a, R = H, 95%
4b, R = Me, 93%

Scheme 2. Synthesis of 2'-fluoroisoflavone 6-hydroxy/alkoxymethyl derivatives.

As we previously reported, 7-hydroxy-8-dimethylaminomethyl/alkoxymethyl isoflavone [16] and phenol [17] derivatives may be used as precursors for the thermally generated *ortho*-quinone methides.

10, 48%

8a, 8b

12, 45%
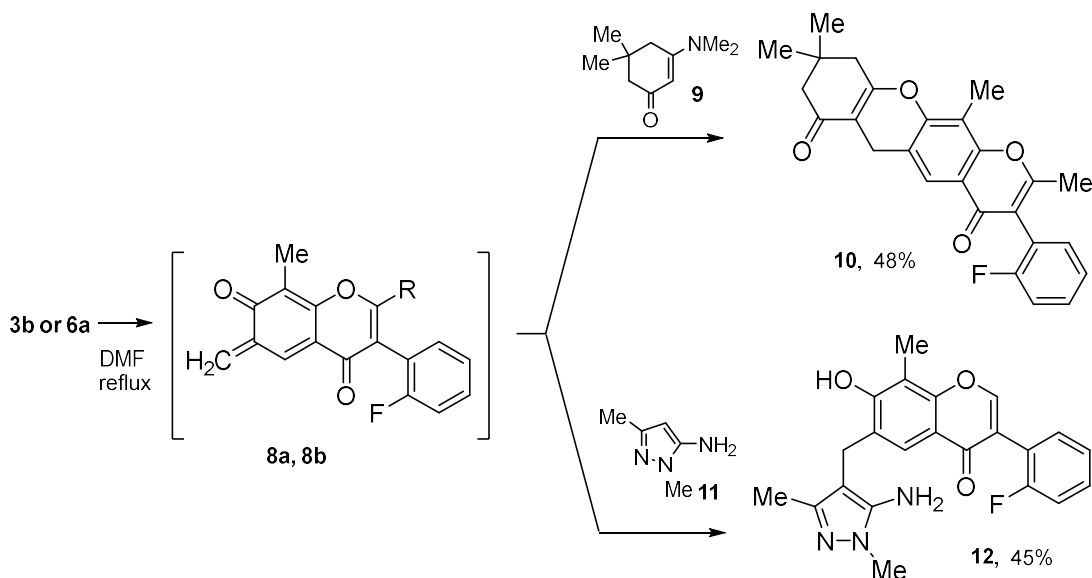
Scheme 3. Appling of 2'-fluoroisoflavones **3b** or **6a** in Diels-Alder reaction and Michael addition.

We expected that synthesized 2'-fluoroisoflavone Mannich bases and 6-alkoxymethyl derivatives also can thermally generate *ortho*-quinone methides **8a** or **8b**. For the trapping of these intermediates we used 3-(*N,N*-dimethylamino)-5,5-dimethylcyclohex-2-

en-1-one (**9**) such as related derivatives of 6-dimethelaminomethyl isoflavones shown promise anticancer activity [16]. The reaction of Mannich base **3b** with enaminone **10** led to the formation of tetracyclic compound **10** *via* formation of *ortho*-quinone methide **8b**, inverse-electron-demand Diels–Alder addition with compound **9**, and resulting elimination of dimethylamine from hetero-Diels-Alder adduct, which afford compond **10**.

Using of electron-rich 5-amino-1,3-dimethylpyrazole (**11**) for the trapping of thermally generated from methoxymethil derivative **6a** *ortho*-quinone methide **9a**, led to the Michael adduct **12** appearance. It should be noted, that reaction was carried out on pyrazole C-4 atom, instead involving of 5-aminogroup (Scheme 3). Such result may be explained by presence of the coordinated electron-donating effects of pyrazole ring and 5-aminogroup.

Conclusions

Simple synthetic methods for the introduction of hydroxymethyl/methoxymethyl group on position 6 of chromone ring have been developed for the B-ring fluorine-containing 7-hydroxyisoflavones. Reaction of the thermally generated *ortho*-quinone methides with 3-(*N,N*-dimethylamino)-5,5-dimethyl-2-cyclohexen-1-one or 1,3-dimethyl-5-aminopyrazole led to the formation of hetero-Diels–Alder or Michael products. Synthesized fluorinated isoflavones

could be useful for the further studies of their anticancer activity.

Experimental part

General

Melting points were determined in open capillarity tubes with a Buchi B-535 apparatus. Reaction completion and chemical purity of the synthesized compounds were controlled by TLC with Macherey-Nagel ALUGRAM Xtra Sil G/UV$_{254}$ plates. Column chromatography was performed using Macherey-Nagel Silica 60, 0.04-0.063 mm silica gel. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a Bruker Avance 500 spectrometer or on a Varian 400 spectrometer in CDCl$_3$ or DMSO-d_6 [residual CHCl$_3$ (δ_H = 7.26 ppm) or CDCl$_3$ (δ_C = 77.16 ppm) as internal reference] or in DMSO-d$_6$ [residual SO(CD$_3$)(CD$_2$H)$_3$ (δ_H = 2.50 ppm) or SO(CD$_3$)$_2$ (δ_C = 39.52 ppm) as internal reference]. CFCl$_3$ (δ_F = 0.00 ppm) was used external reference for ^{19}F NMR spectra. LC/MS (APCI) spectra were recorded on Agilent 1100 LC MS (APCI) SL instrument, column SUPELCO Ascentis Express C18.

1-(2,4-Dihydroxy-3-methylphenyl)-2-(2-fluorophenyl)ethanone (1). A solution of 13.6 g (0.11 mol) 2-methylresorcinol, 13.5 g (0.1 mol) of the (2-fluorophenyl)acetonitrile in 80 mL of boron trifluoride etherate was saturated by bubbling of gaseous dry HCl over a 6h period at ambient temperature. The mixture was poured into 500 mL of water at 80°C. Then, the resulting mixture was heated to reflux for 2h, cooled to

ambient temperature. The formed solid was filtered off and recrystallized from mixture of MeOH-H_2O. Yield: 15.0 g (58%); white solid; m.p. 150 – 152 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.80 (s, 1H), 10.64 (s, 1H), 7.82 (d, $J =$ 8.9 Hz, 1H), 7.41 – 7.27 (m, 2H), 7.24 – 7.05 (m, 2H), 6.54 (d, $J =$ 8.9 Hz, 1H), 4.40 (s, 2H), 2.00 (s, 3H) ppm. ^{13}C NMR (125 MHz, DMSO-d_6): δ 200.92, 162.83, 162.47, 160.81 (d, $J_{(C,F)} =$ 244.3 Hz), 132.33 (d, $J_{(C,F)} =$ 4.6 Hz), 129.72, 128.94 (d, $J_{(C,F)} =$ 8.1 Hz), 124.26 (d, $J_{(C,F)} =$ 3.3 Hz), 122.36 (d, $J_{(C,F)} =$ 16.1 Hz), 115.00 (d, $J_{(C,F)} =$ 21.5 Hz), 111.60, 110.48, 107.43, 37.73, 7.59 ppm. ^{19}F NMR (376 MHz, DMSO-d_6): δ -116.7 ppm. MS (APCI): calcd for $C_{15}H_{14}FO_3^+$ [M+H]$^+$: 261.1 *m/z*, found: 261.2 *m/z*.

3-(2-Fluorophenyl)-7-hydroxy-8-methyl-4*H*-chromen-4-one (2a).

To a solution of 1.3 g (0.05 mol) deoxybenzoin **1** in 10 mL of *N,N*-dimethylformamide at 30-40 °C boron trifluoride etherate (1.9 mL, 0.15 mol) was added. After the mixture was stirred for 0.5 h, the phosphorous oxytrichloride (1.86 mL, 0.1 mol) was added at the same temperature. The mixture was heated at 55-60°C for 2 h than was poured into 50 mL of boiling water with vigorous stirring and then cooled. The formed precipitate was filtered off, washed with water and recrystallized from methanol. Yield: 0.99g, (73%) white solid; m.p. 287 – 289 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.73 (s, 1H), 8.41 (s, 1H), 7.82 (d, $J =$ 8.7 Hz, 1H), 7.55 – 7.39 (m, 2H), 7.32 – 7.22 (m, 2H), 7.03 (d, $J =$ 8.7 Hz,

1H), 2.24 (s, 3H) ppm. ^{13}C {^{1}H} NMR (125 MHz, DMSO-d_6): δ 174.09, 160.25, 160.12 (d, $J_{(C,F)} =$ 246.5 Hz), 155.67, 154.68 , 132.24 (d, $J_{(C,F)} =$ 3.3 Hz), 130.17 (d, $J_{(C,F)} =$ 8.2 Hz), 124.17 (d, $J_{(C,F)} =$ 3.2 Hz), 123.70, 120.12 (d, $J_{(C,F)} =$ 15.6 Hz), 119.15, 116.37, 115.41 (d, $J_{(C,F)} =$ 21.9 Hz), 114.12, 111.15, 7.98 ppm. ^{19}F {^{1}H} NMR (376 MHz, DMSO-d_6): δ -114.8 ppm. MS (APCI): calcd for $C_{16}H_{12}FO_3^+$ [M+H]$^+$: 271.1 *m/z,* found: 271.0 *m/z*.

3-(2-Fluorophenyl)-7-hydroxy-2,8-dimethyl-4*H*-chromen-4-one (2b).

To a solution of 1.3 g (0.05 mol) deoxybenzoin **1** in 10 mL of *N,N*-dimethylacetamide at 30-40 °C boron trifluoride (1.9 mL, 0.15 mol) was added. After the mixture was stirred for 0.5 h, the phosphorous oxytrichloride (1.86 mL, 0.1 mol) was added at the same temperature. The mixture was heated at 55-60°C for 6-8 h, than was poured into 50 mL of hot water with vigorous stirring and then cooled. The formed precipitate was filtered off, washed with water and recrystallized from methanol. Yield: 0.80 g, (56%); pale yellow powder; m.p. 321 – 323 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.62 (s, 1H), 7.72 (d, $J =$ 8.7 Hz, 1H), 7.45 – 7.37 (m, 1H), 7.34 – 7.28 (m, 1H), 7.27 – 7.20 (m, 2H), 6.96 (d, $J =$ 8.7 Hz, 1H), 2.21 (s, 3H), 2.20 (s, 3H) ppm. ^{13}C {^{1}H} NMR (125 MHz, DMSO-d_6): δ 174.59, 163.17, 160.09, 159.89 (d, $J_{(C,F)} =$ 244.6 Hz), 155.18, 132.78 (d, $J_{(C,F)} =$ 3.4 Hz), 130.07 (d, $J_{(C,F)} =$ 8.2 Hz), 124.20 (d, $J_{(C,F)} =$ 3.5 Hz), 123.51, 121.13 (d, $J_{(C,F)} =$ 16.5 Hz), 116.28, 115.39 (d, $J_{(C,F)} =$ 22.0 Hz), 115.20,

113.73, 110.75, 18.92, 7.93 ppm. ^{19}F $\{^1H\}$ NMR (376 MHz, CDCl$_3$): δ -113.8 ppm. MS (APCI): calcd for C$_{17}$H$_{14}$FO$_3^+$ [M+H]$^+$: 285.1 *m/z*, found: 285.2 *m/z*.

General procedure for the synthesis of Mannich bases 3a, 3b. To a suspension of 5 mmol of isoflavone **2a** or **2b** in 30 mL of 1,4-dioxane, 1.4 mL (10 mmol) of bis(*N,N*-dimethylamino)methane at 70°C was added. The mixture was heated at 100°C for 16 h, cooled, and diluted with hexane. The formed precipitate was collected to afford Mannich bases of **3a, 3b**.

6-[(Dimethylamino)methyl]-3-(2-fluorophenyl)-7-hydroxy-8-methyl-4*H*-chromen-4-one (3a). Yield: 1.51 g (92%); white solid; m.p. 149 – 151 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.03 (s, 1H), 7.82 (s, 1H), 7.52 – 7.45 (m, 1H), 7.41 – 7.33 (m, 1H), 7.25 – 7.13 (m, 2H), 3.79 (s, 2H), 2.37 (s, 6H), 2.33 (s, 3H) ppm. ^{13}C $\{^1H\}$ NMR (125 MHz, CDCl$_3$): δ 175.48, 161.65, 160.40 (d, $J_{(C,F)}$ = 247.6 Hz), 155.86, 154.03 (d, $J_{(C,F)}$ = 2.7 Hz), 132.15 (d, $J_{(C,F)}$ = 2.6 Hz), 129.87 (d, $J_{(C,F)}$ = 8.2 Hz), 124.03 (d, $J_{(C,F)}$ = 3.3 Hz), 122.80, 120.56, 120.02 (d, $J_{(C,F)}$ = 14.9 Hz), 119.43, 116.59, 115.82 (d, $J_{(C,F)}$ = 22.3 Hz), 112.07, 62.40, 44.26, 7.90 ppm. ^{19}F $\{^1H\}$ NMR (470 MHz, CDCl$_3$): δ -114.8 ppm. MS (APCI): calcd for C$_{19}$H$_{19}$FNO$_3^+$ [M+H]$^+$: 328.1 *m/z*, found: 328.2 *m/z*.

6-[(Dimethylamino)methyl]-3-(2-fluorophenyl)-7-hydroxy-2,8-dimethyl-4*H*-chromen-4-one (3b). Yield: 1.49 g (87%); beige solid; m.p. 177 – 179 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.73 (s, 1H), 7.39 – 7.32 (m, 1H), 7.31 – 7.27 (m, 1H), 7.23 – 7.18 (m, 1H), 7.17 – 7.11 (m, 1H), 3.76 (s, 2H), 2.35 (s, 6H), 2.32 (s, 3H), 2.29 (s, 3H) ppm. ^{13}C $\{^1H\}$ NMR (100 MHz, CDCl$_3$): δ 176.28, 163.49, 161.43, 160.43 (d, $J_{(C,F)}$ = 246.1 Hz), 155.58, 132.80 (d, $J_{(C,F)}$ = 3.3 Hz), 129.91 (d, $J_{(C,F)}$ = 8.2 Hz), 124.12 (d, $J_{(C,F)}$ = 3.5 Hz), 122.78, 121.29 (d, $J_{(C,F)}$ = 16.5 Hz), 120.20, 116.93, 115.84 (d, $J_{(C,F)}$ = 22.3 Hz), 115.47, 111.71, 62.52, 44.37, 19.44, 8.01 ppm. ^{19}F $\{^1H\}$ NMR (376 MHz, CDCl$_3$): δ -115.2 ppm. MS (APCI): calcd for C$_{20}$H$_{21}$FNO$_3^+$ [M+H]$^+$: 342.2 *m/z*, found: 342.2 *m/z*.

General procedure for the synthesis of diacetates 4a, 4b. A mixture of a Mannich base **3a** or **3b** (2 mmol) and 200 mg (2 mmol) of potassium acetate in 5 mL of acetic anhydride was refluxed for 5 min and cooled to room temperature. The mixture was diluted with water to form a precipitate of **5a,b** respectively, which was recrystallized from acetonitrile-water.

[7-(Acetyloxy)-3-(2-fluorophenyl)-8-methyl-4-oxo-4*H*-chromen-6-yl]methyl acetate (4a). Yield: 365 mg (95%); white solid; m.p. 120 – 122 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.22 (s, 1H), 8.08 (s, 1H), 7.46 (t, J = 7.4 Hz, 1H), 7.41 – 7.31 (m, 1H), 7.24 – 7.08 (m, 2H), 5.13 (s, 2H), 2.39 (s, 3H), 2.29 (s, 3H), 2.07 (s, 3H) ppm. ^{13}C $\{^1H\}$ NMR (125 MHz, CDCl$_3$): δ 175.12, 170.52, 168.17, 160.29 (d, $J_{(C,F)}$ = 248.0 Hz), 155.12, 154.63, 154.61, 151.53, 132.00 (d, $J_{(C,F)}$ = 2.8 Hz), 130.31 (d, $J_{(C,F)}$ = 8.2 Hz), 126.65, 125.16, 124.15 (d, $J_{(C,F)}$ = 3.5 Hz), 122.30, 121.39,

120.31, 119.17 (d, $J_{(C,F)}$ = 14.8 Hz), 115.90 (d, $J_{(C,F)}$ = 22.2 Hz), 61.31, 20.83, 20.50, 9.48 ppm. ^{19}F {^{1}H} NMR (376 MHz, CDCl$_3$): δ -114.7 ppm. MS (APCI): calcd for C$_{21}$H$_{18}$FO$_6^+$ [M+H]$^+$: 385.1 *m/z*, found: 385.0 *m/z*.

[7-(Acetyloxy)-3-(2-fluorophenyl)-2,8-dimethyl-4-oxo-4*H*-chromen-6-yl]methyl acetate (4b). Yield: 371 mg (93%); white solid; m.p. 144 – 146 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.15 (s, 1H), 7.40 – 7.32 (m, 1H), 7.30 – 7.24 (m, 1H), 7.23 – 7.17 (m, 1H), 7.13 (t, *J* = 8.9 Hz, 1H), 5.11 (s, 2H), 2.38 (s, 3H), 2.31 (s, 3H), 2.29 (s, 3H), 2.06 (s, 3H) ppm. ^{13}C {^{1}H} NMR (125 MHz, CDCl$_3$): δ 175.63, 170.45, 168.16, 164.34, 160.21 (d, $J_{(C,F)}$ = 246.6 Hz), 154.78, 151.32, 132.50 (d, $J_{(C,F)}$ = 3.0 Hz), 130.18 (d, $J_{(C,F)}$ = 8.2 Hz), 126.12, 125.04, 124.12 (d, $J_{(C,F)}$ = 3.4 Hz), 121.07, 120.81, 120.40 (d, $J_{(C,F)}$ = 16.3 Hz), 117.81, 115.78 (d, $J_{(C,F)}$ = 22.1 Hz), 61.31, 20.79, 20.47, 19.35, 9.44 ppm. ^{19}F {^{1}H} NMR (376 MHz, CDCl$_3$): δ -114.8 ppm. MS (APCI): calcd for C$_{22}$H$_{20}$FO$_6^+$ [M+H]$^+$: 399.1 *m/z*, found: 399.0 *m/z*.

General procedures for the synthesis of hydroxymethyl derivatives 5a, 5b. A solution of compound **4a, 4b** (1 mmol) in 10 mL of 1,4-dioxane and 20 mL of 0.2 M aqueous sulfuric acid was heated at 50-60°C for 6-8 h. The mixture was cooled and diluted with 30 mL water, the resulting precipitate was filtered off. The crude product was chromatographed using 1:20 methanol-dichloromethane mixture as eluent to afford **6a,b,** recrystallized from acetonitrile.

3-(2-Fluorophenyl)-7-hydroxy-6-(hydroxymethyl)-8-methyl-4*H*-chromen-4-one (5a). Yield: 150 mg (50%); white solid; m.p. 177 – 179 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.80 (s, 1H), 8.44 (s, 1H), 7.94 (s, 1H), 7.54 – 7.37 (m, 3H), 7.34 – 7.17 (m, 2H), 4.64 (s, 2H), 2.30 (s, 3H). ^{13}C {^{1}H} NMR (125 MHz, DMSO-d_6): δ 174.16, 160.13 (d, $J_{(C,F)}$ = 246.4 Hz), 157.25, 154.66, 154.52, 132.27, 130.20 (d, $J_{(C,F)}$ = 8.0 Hz), 128.33, 124.24, 120.75, 120.21 (d, $J_{(C,F)}$ = 15.6 Hz), 119.26, 116.32, 115.46 (d, $J_{(C,F)}$ = 21.9 Hz), 111.39, 59.07, 8.46 ppm. ^{19}F {^{1}H} NMR (470 MHz, DMSO-d_6): δ -113.7 ppm. MS (APCI): calcd for C$_{17}$H$_{14}$FO$_4^+$ [M+H]$^+$: 301.1 *m/z*, found: 301.2 *m/z*.

3-(2-Fluorophenyl)-7-hydroxy-6-(hydroxymethyl)-2,8-dimethyl-4*H*-chromen-4-one (5b). Yield: 176 mg (56%); white solid; m.p. 186 – 188 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.69 (s, 1H), 7.86 (s, 1H), 7.52 – 7.38 (m, 1H), 7.38 – 7.19 (m, 3H), 5.43 (s, 1H), 4.64 (s, 2H), 2.31 (s, 3H), 2.25 (s, 3H) ppm. ^{13}C {^{1}H} NMR (125 MHz, DMSO-d_6): δ 174.64, 163.12, 159.87 (d, $J_{(C,F)}$ = 244.5 Hz), 157.06, 154.01, 132.77, 130.10 (d, $J_{(C,F)}$ = 8.1 Hz), 127.88, 124.24, 121.18 (d, $J_{(C,F)}$ = 16.5 Hz), 120.63, 116.40, 115.43 (d, $J_{(C,F)}$ = 21.9 Hz), 115.11, 111.01, 59.04, 19.00, 8.41 ppm. ^{19}F {^{1}H} NMR (470 MHz, DMSO-d_6): δ -113.6 ppm. MS (APCI): calcd for C$_{18}$H$_{16}$FO$_4^+$ [M+H]$^+$: 315.1 *m/z*, found: 315.2 *m/z*.

General procedures for the synthesis of alkoxymethyl derivatives 6 − 7. A mixture of

diacetate **4a** or **4b** (2 mmol) and 0.1 mL of concentrated hydrochloric acid in 10 mL of methanol or ethanol was refluxed for 16-24 h. The mixture was cooled and diluted with water, the resulting precipitate was filtered off. The products **6a,b** and **7a,b** were purified by column chromatography using 1:20 methanol-dichloromethane mixture as eluent.

3-(2-Fluorophenyl)-7-hydroxy-6-(methoxymethyl)-8-methyl-4*H*-chromen-4-one (6a). Yield: 242 mg (77%); white solid; m.p. 143 – 145 ºC. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.79 (s, 1H), 8.40 (s, 1H), 7.86 (s, 1H), 7.57 – 7.35 (m, 2H), 7.25 (q, J = 7.4, 6.9 Hz, 2H), 4.52 (s, 2H), 3.34 (s, 3H), 2.28 (s, 3H) ppm. ^{13}C $\{^1$H$\}$ NMR (125 MHz, DMSO-d_6): δ 174.07, 160.09 (d, $J_{(C,F)}$ = 246.4 Hz), 157.52, 154.83, 154.72, 132.22, 130.20 (d, $J_{(C,F)}$ = 8.0 Hz), 124.62, 124.18, 122.21, 120.08 (d, $J_{(C,F)}$ = 15.6 Hz), 119.25, 116.28, 115.42 (d, $J_{(C,F)}$ = 21.9 Hz), 111.82, 69.13, 57.79, 8.55 ppm. ^{19}F $\{^1$H$\}$ NMR (470 MHz, DMSO-d_6): δ -113.46 ppm. ^{19}F $\{^1$H$\}$ NMR (470 MHz, CDCl$_3$): δ -113.5 ppm. MS (APCI): calcd for C$_{18}$H$_{16}$FO$_4^+$ [M+H]$^+$: 315.1 *m/z*, found: 315.2 *m/z*.

3-(2-Fluorophenyl)-7-hydroxy-6-(methoxymethyl)-2,8-dimethyl-4*H*-chromen-4-one (6b). Yield: 256 mg (78%); white solid; m.p. 159 – 161 ºC. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.67 (s, 1H), 7.79 (s, 1H), 7.46 – 7.39 (m, 1H), 7.34 – 7.21 (m, 3H), 4.51 (s, 2H), 3.33 (s, 3H), 2.30 (s, 3H), 2.22 (s, 3H) ppm. ^{13}C $\{^1$H$\}$ NMR (125 MHz, DMSO-d_6): δ 174.59, 163.25,

159.88 (d, $J_{(C,F)}$ = 244.7 Hz), 157.40, 154.37, 132.77 (d, $J_{(C,F)}$ = 3.0 Hz), 130.10 (d, $J_{(C,F)}$ = 8.2 Hz), 124.23 (d, $J_{(C,F)}$ = 3.0 Hz), 124.17, 122.17, 121.09 (d, $J_{(C,F)}$ = 16.5 Hz), 116.42, 115.42 (d, $J_{(C,F)}$ = 22.0 Hz), 115.12, 111.45, 69.18, 57.74, 18.94, 8.51 ppm. ^{19}F $\{^1$H$\}$ NMR (470 MHz, DMSO-d_6): δ -113.7 ppm. MS (APCI): calcd for C$_{19}$H$_{18}$FO$_4^+$ [M+H]$^+$: 329.1 *m/z*, found: 329.0 *m/z*.

6-(Ethoxymethyl)-3-(2-fluorophenyl)-7-hydroxy-8-methyl-4*H*-chromen-4-one (7a). Yield: 250 mg (76%); white solid; m.p. 136 – 138 ºC. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.77 (s, 1H), 8.41 (s, 1H), 7.87 (s, 1H), 7.48 – 7.38 (m, 2H), 7.29 – 7.21 (m, 2H), 4.56 (s, 2H), 3.54 (q, J = 6.8 Hz, 2H), 2.29 (s, 3H), 1.17 (d, J = 6.8 Hz, 3H) ppm. ^{13}C $\{^1$H$\}$ NMR (125 MHz, DMSO-d_6): δ 174.50, 160.52 (d, $J_{(C,F)}$ = 246.4 Hz), 157.88, 155.19, 155.16, 132.65 (d, $J_{(C,F)}$ = 3.1 Hz), 130.63 (d, $J_{(C,F)}$ = 8.2 Hz), 125.42, 124.62 (d, $J_{(C,F)}$ = 3.1 Hz), 122.43, 120.52 (d, $J_{(C,F)}$ = 15.6 Hz), 119.68, 116.72, 115.85 (d, $J_{(C,F)}$ = 21.9 Hz), 112.18, 67.58, 65.77, 15.56, 8.98 ppm. ^{19}F $\{^1$H$\}$ NMR (470 MHz, DMSO-d_6): δ -113.5 ppm. MS (APCI): calcd for C$_{19}$H$_{18}$FO$_4^+$ [M+H]$^+$: 329.1 *m/z*, found: 329.0 *m/z*.

6-(Ethoxymethyl)-3-(2-fluorophenyl)-7-hydroxy-2,8-dimethyl-4*H*-chromen-4-one (7b). Yield: 284 mg (83%); white solid; m.p. 146 – 148 ºC. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.67 (s, 1H), 7.81 (s, 1H), 7.45 (d, J = 6.1 Hz, 1H), 7.38 – 7.18 (m, 3H), 4.57 (s, 2H), 3.55 (d, J = 6.9 Hz, 2H), 2.32 (s, 3H), 2.25 (s, 3H), 1.18 (t, J =

6.9 Hz, 3H) ppm. ^{13}C $\{^{1}$H$\}$ NMR (125 MHz, DMSO-d_6): δ 174.59, 163.25, 159.87 (d, $J_{(C,F)}$ = 244.7 Hz), 157.32, 154.30, 132.77 (d, $J_{(C,F)}$ = 2.9 Hz), 130.12 (d, $J_{(C,F)}$ = 8.1 Hz), 124.55, 124.24 (d, $J_{(C,F)}$ = 2.9 Hz), 121.96, 121.09 (d, $J_{(C,F)}$ = 16.4 Hz), 116.42, 115.42 (d, $J_{(C,F)}$ = 22.0 Hz), 115.12, 111.39, 67.19, 65.29, 18.97, 15.13, 8.52 ppm. ^{19}F $\{^{1}$H$\}$ NMR (470 MHz, DMSO-d_6): δ -113.4 ppm. MS (APCI): calcd for $C_{20}H_{20}FO_4^+$ [M+H]$^+$: 343.1 *m/z*, found: 343.2 *m/z*.

3-(2-Fluorophenyl)-2,9,9,12-tetramethyl-6,8,9,10-tetrahydro-4*H*,7*H*-pyrano[3,2-*b*]xanthene-4,7-dione (10). To a solution of 340 mg (1 mmol) compound **3b** 209 mg (1.25 mmol) of 3-(*N*,*N*-dimethylamino)-5,5-dimethylcyclohex-2-en-1-one [18] (**9**) in 10 mL of DMF was added. The solution was refluxed for 4 h, diluted with 20 mL of methanol, the formed precipitate was filtered off and recrystallized from DMF-methanol to afford compound **10**. Yield: 201 mg (48%); white solid; m.p. 249 – 250 ºC. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.88 (s, 1H), 7.41 – 7.34 (m, 1H), 7.31 – 7.26 (m, 1H), 7.25 – 7.19 (m, 1H), 7.18 – 7.12 (m, 1H), 3.61 (s, 2H), 2.52 (s, 2H), 2.40 (s, 3H), 2.35 (s, 2H), 2.32 (s, 3H), 1.16 (s, 6H) ppm. ^{13}C $\{^{1}$H$\}$ NMR (100 MHz, CDCl$_3$): δ 197.70, 175.81, 164.23, 164.05, 160.33 (d, $J_{(C,F)}$ = 246.5 Hz), 153.76, 151.53, 132.67 (d, $J_{(C,F)}$ = 3.2 Hz), 130.15 (d, $J_{(C,F)}$ = 8.0 Hz), 124.20, 124.16 (d, $J_{(C,F)}$ = 3.3 Hz), 120.74 (d, $J_{(C,F)}$ = 16.3 Hz), 119.69, 118.71, 117.45, 115.88 (d, $J_{(C,F)}$ = 22.2 Hz), 113.97, 109.27, 50.73, 41.41, 32.31, 28.58

(d, $J_{(C,F)}$ = 2.7 Hz), 21.08, 19.51, 8.46 ppm. ^{19}F $\{^{1}$H$\}$ NMR (376 MHz, CDCl$_3$): δ -114.2 ppm. MS (APCI): calcd for $C_{26}H_{24}FO_4^+$ [M+H]$^+$: 419.2 *m/z*, found: 419.2 *m/z*.

6-[(5-Amino-1,3-dimethyl-1*H*-pyrazol-4-yl)methyl]-3-(2-fluorophenyl)-7-hydroxy-8-methyl-4*H*-chromen-4-one (12). To a solution of 314 mg (1 mmol) of compound **6a** 223 mg (2 mmol) of 5-amino-1,3-dimethylpyrazole in 10 mL of DMF was added. The solution was refluxed for 4 h. Then, the mixture was diluted with 20 mL of methanol, the formed precipitate was filtered off and recrystallized from DMF-methanol to afford compound **12**. Yield: 177 mg, (45%); white solid; m.p. 265 – 267 ºC. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.77 (s, 1H), 8.41 (s, 1H), 7.44 (s, 1H), 7.43 – 7.37 (m, 2H), 7.30 – 7.21 (m, 2H), 4.93 (s, 2H), 3.61 (s, 2H), 3.48 (s, 3H), 2.33 (s, 3H), 1.83 (s, 3H) ppm. ^{13}C $\{^{1}$H$\}$ NMR (100 MHz, DMSO-d_6): δ 174.01, 160.05 (d, $J_{(C,F)}$ = 246.3 Hz), 157.91, 154.50, 153.94, 144.54, 144.22, 132.19 (d, $J_{(C,F)}$ = 3.3 Hz), 130.11 (d, $J_{(C,F)}$ = 8.2 Hz), 127.95, 124.13 (d, $J_{(C,F)}$ = 3.3 Hz), 121.80, 120.18 (d, $J_{(C,F)}$ = 15.7 Hz), 119.10, 116.27, 115.36 (d, $J_{(C,F)}$ = 21.9 Hz), 111.20, 96.56, 33.95, 22.69, 12.13, 8.75 ppm. ^{19}F $\{^{1}$H$\}$ NMR (470 MHz, DMSO-d_6): δ -113.6 ppm. MS (APCI): calcd for $C_{22}H_{21}FN_3O_3^+$ [M+H]$^+$: 394.2 *m/z*, found: 394.2 *m/z*.

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