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SYNTHESIS OF 2-TRIFLUOROACETONYL-3-ALKYL/ALKOXY-CHROMONES AND THEIR REACTIONS WITH 1,2-BIDENTATE NUCLEOPHILES

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Abstract – The reaction of 3-substituted 2-methyl/2-benzyl/2-(2-phenethyl)-chromones with trifluoroacetic anhydride in presence of potassium trifluoroacetate was investigated. It was established that the nature of substituent in position 3 of chromone ring has no crucial influence/limitation on this reaction, whereas only in the case of 2-benzyl substituent (in addition to 2-*sec*-alkyl group) no reaction was occurred at all. Reaction of synthesized 2-(3,3,3-trifluoro-2-oxopropyl)chromones with hydrazine dihydrochloride afforded 3-(2-hydroxyphenacyl)-5-trifluoro-methylpyrazoles, but reaction with hydroxylamine led to oximation of side-chain carbonyl group. Reaction of 2-trifluoromethylchromones with 1,2-bidentate nucleophiles led to substituted 2-hydroxyphenylpyrazoles and isoxazoles. Mechanisms of these ring-transformation reactions are discussed.

INTRODUCTION

Due to presence of two electron-deficient centers in chromone core, reaction of chromones with nucleophiles may be attributed to important strategy for construction of various heterocycles. Usually, initial attack of bidentate nucleophiles passed out on C-2 chromone atom with further cleavage of pyranone ring afforded to the formation of various heterocyclic system.[1] These reactions are more useful in the case of 3-arylchromones (isoflavones), since the absence of bulky C-2 substituent is allowed to pass reactions chemoselectively with bidentate nucleophiles. However, reaction of 2-unsubstituted chromones with hydroxylamine or mono substituted hydrazine derivatives usually is non-selective and resulted in formation of regioisomeric isoxazoles and pyrazoles mixtures. The presence of bulky C-2 substituent can fully

deactivate chromones to react with these nucleophiles. Moreover, presence of substituent(s) in position 2 or 3 of chromone ring, bearing extra nucleophilic center, could be fundamental reason for the initial attack of nucleophiles which led to salicyloyl or phenacyl heterocycles with intact carbonyl group of chromone ring.

The introduction of strong electron withdrawing trifluoromethyl group in chromone core may bring perturbation on nucleophilic centers resulted in some another chemical behavior of chromones toward nucleophiles. For example, reaction of 2-trifluoroacetylchromones with anilines notably depends on their nucleophilicity and could be carried out as C or N nucleophiles.[2]

As we recently reported, reaction of 2,3-dimethylchromones with trifluoroacetic anhydride in presence of potassium trifluoroacetate led to selective trifluoroacetylation of 2-methyl group and formation of 2-(3,3,3-trifluoroacetonyl)-3-methylchromone and its 7-hydroxyderivative.[3] The related 2-thifluoroacetonylisoflavones were established as promising compounds for the synthesis of 3-trifluoromethylpyrazoles.[4]

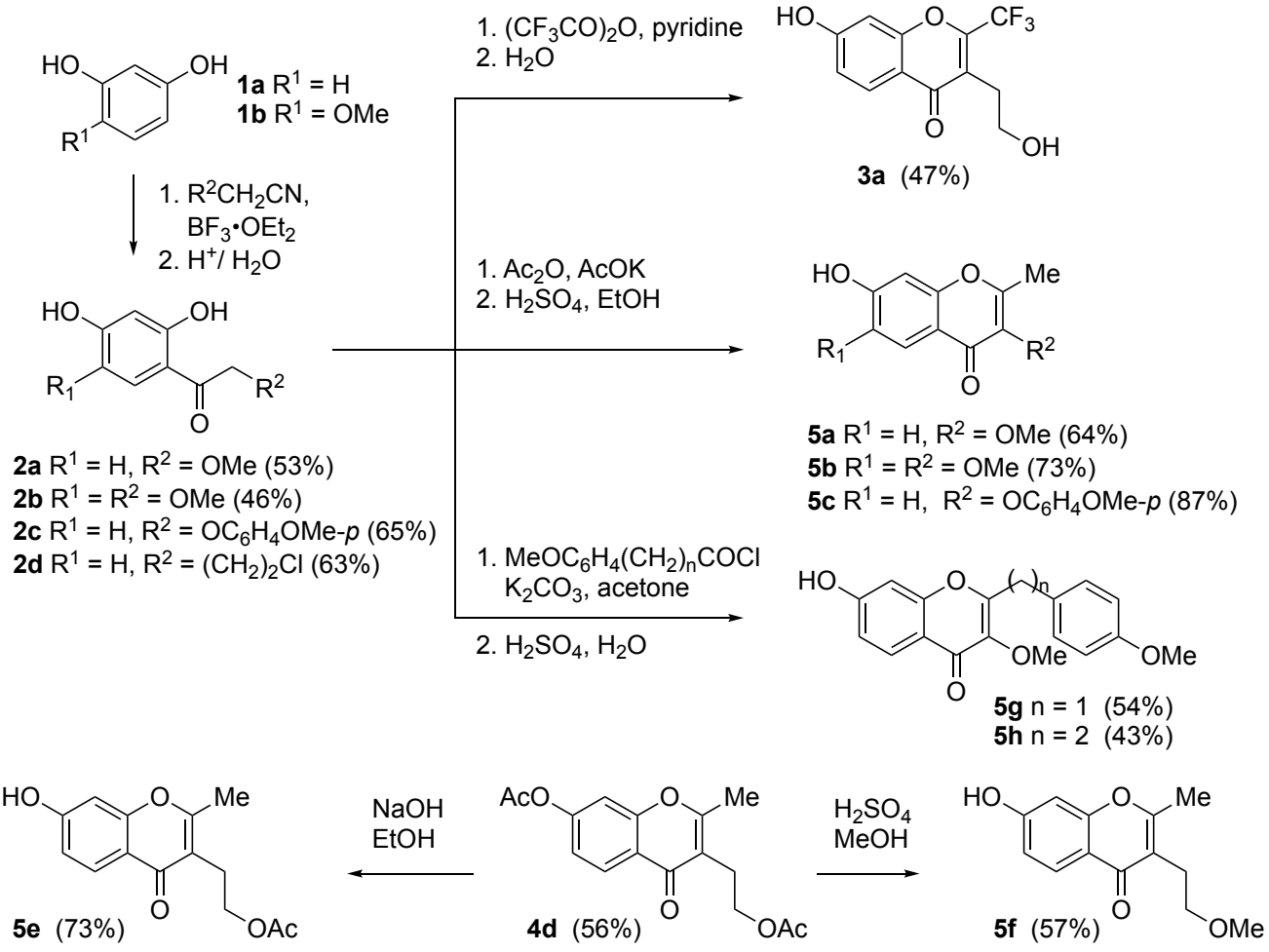
In this work we focused on the synthesis of 3-substituted chromones with trifluoromethyl or 3,3,3-trifluoro-2-oxopropyl group in position 2 of chromone ring and their reaction with 1,2-bidentate nucleophiles such as hydrazine and hydroxylamine derivatives. In addition to recently reported 3-phenylchromones (isoflavones),[4] in current investigation we paid more attention on the preparation of chromones bearing methyl, hydroxyethyl, and methoxy/aryloxy substituent in the position 3 of chromone core. It should be noted that the main goal was to study the behavior of 2-fluoroakylchromones with 1,2-bidentate nucleophiles. Moreover, synthetic application area of 2-alky/arylakylchromones in trifluoroacetylation reactions is also necessary to clarify.

RESULTS AND DISCUSSION

Thus, reaction of resorcinol (**1a**) and 4-methoxyresorcinol (**1b**) with substituted acetonitriles in presence of HCl in the boron trifluoride etherate media followed by subsequent acidic hydrolysis of intermediate ketoimine hydrochlorides led to formation of ketones **2a-d** in moderate yield. Reaction of chloropropyl-ketone **2d** with trifluoroacetic anhydride in pyridine with subsequent hydrolysis of trifluoroacetoxychromone led to afford 2-trifluoromethyl-3-(2-hydroxyethyl)chromone **3a** in 47% yield.

Synthesized ketones **2a-c** were converted to 2-methylchromones **5a-c** using heating of these compounds with acetic anhydride in presence of AcOK with subsequent hydrolysis of intermediate acetates, which were used without purification and identification. In case of 4-chloropropylketone **2d** formed diacetate **4d** was transformed to 3-(3-acetoxyethyl)chromone **5e** when reacted with NaOH in EtOH, while acidic hydrolysis in MeOH afforded 3-(3-methoxyethyl) derivative **5f**. On the other hand, *p*-methoxybenzyl- and

p-methoxyphenetylchromones **5g** and **5h** were obtained by ring-closure reaction of ketone **2a** with 4-methoxyphenylacetyl chloride or 3-(4-methoxyphenyl)propionyl chloride in acetone in presence of K_2CO_3 (Scheme 1). These compounds were selected as model compounds for the clarifying of the synthetic application area of the trifluoroacetylation reaction between 2-alkyl/arylalkylchromones and trifluoroacetic anhydride.



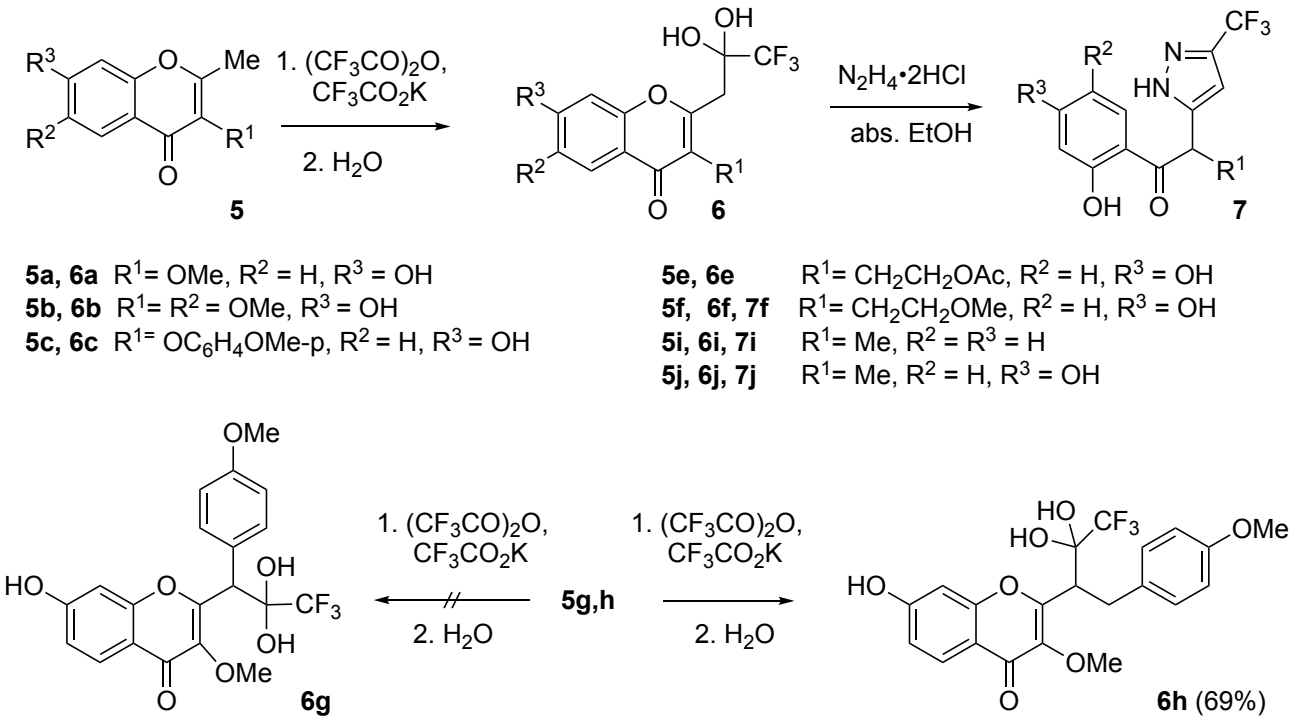
Scheme 1. Synthesis of and 2-thifluoromethyl-, 2-methyl-, and 2-(4-anisylalkyl)chromones

As it was previously reported,[3] trifluoroacetylation of 2-alkylchromones probably underwent via *in situ* formation of vinyl ether and subsequent addition of trifluoroacetic anhydride followed by elimination of trifluoroacetic acid. In the case of reaction of 3-methoxy/*p*-methoxyphenoxy-2-methylchromones **5a-c** and 3-oxyethylchromones **5e**,**f** with trifluoroacetic anhydride in presence of potassium trifluoroacetate, the formation of corresponding 2-(3,3,3-trifluoro-2-oxopropyl)chromones **6a-c**, and **6e**,**f** with moderate to good yields was observed. Reaction of 2-(4-methoxybenzyl)chromone **5g** under similar condition was not successful: only unchanged chromone was isolated from the reaction mixture (Scheme 2). At the same time, when 2-(4-methoxyphenethyl)chromone **5h** was applied, the target fluorinated compound **6h** was obtained in good yield. Probably, the presence of 1-phenyl group conversely to 1-methyl/benzyl group in

intermediate vinyl ether, makes further trifluoroacetylation of chromone-based vinyl ether impossible. All synthesized compounds **6** were identified as *gem*-diols due to signal of carbon atom at 92.3–93.6 ppm in ^{13}C NMR spectra.

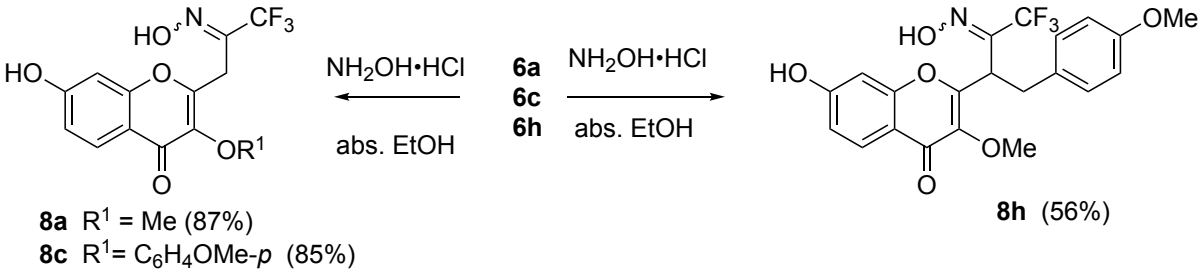
Eventually, 2-benzylchromones similarly to 2-*sec*-alkylchromones do not undergo trifluoroacetylation of 2-CH_2/2-CH_3 group and the nature of C-3 substituent has no crucial influence/limitation on this reaction.

Likewise to 2-(3,3,3-trifluoro-2-oxopropyl)isoflavones, reaction of synthesized compounds **6** in EtOH with hydrazine hydrate did not lead to formation of 3-trifluoromethylpyrazoles. Reaction of 3-methoxy/(*p*-methoxyphenoxy)chromones **6a-c** with hydrazine dihydrochloride in anhydrous EtOH led to the formation of the complex mixtures and isolation of expected 3-trifluoromethylpyrazoles was unsuccessful. But 3-(2-methoxymethyl)chromone **6f**, 3-methylchromones **6i**,**j**[3] easily reacted with hydrazine dihydrochloride to form 3(5)-trifluoromethylpyrazoles **7f-j** (Scheme 2) in moderate to good yields.



Scheme 2. Trifluoroacetylation of 2-methyl/bezyl/phenethylchromones and reaction with hydrazine dihydrochloride

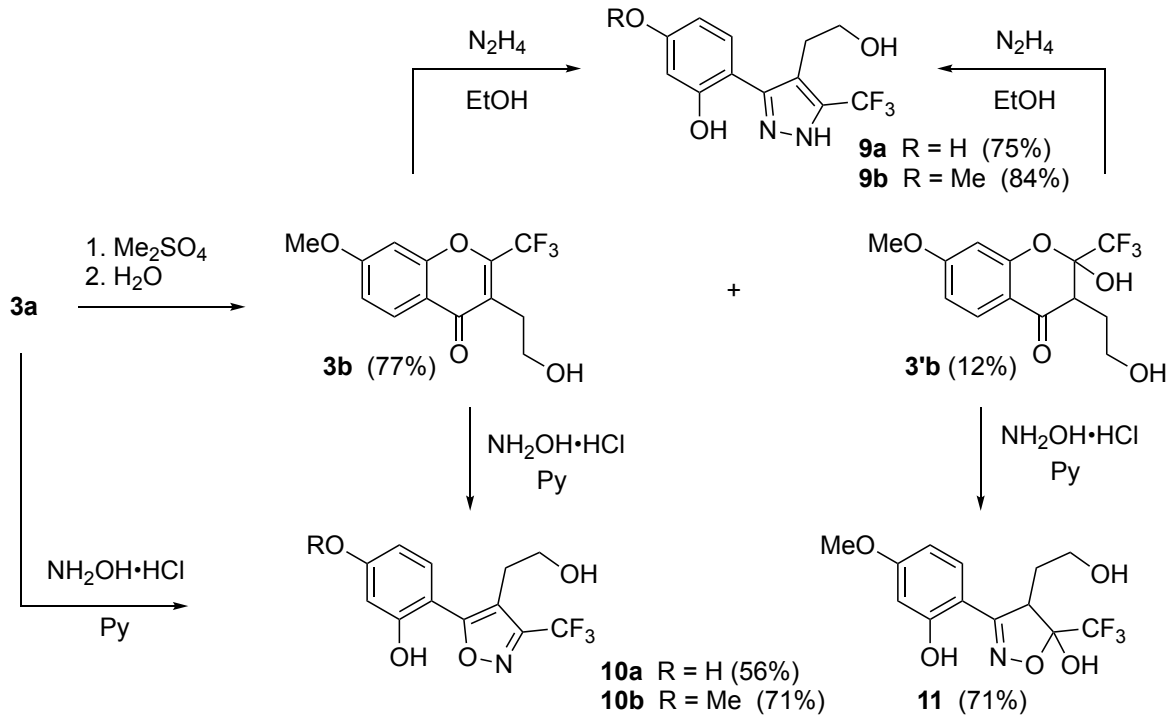
The reaction of 3-methoxy/phenoxychromones **6a**,**c** or **6h** with hydroxylamine hydrochloride in anhydrous EtOH led to the formation of their oximes **8a**,**c** and **8h** in moderate to good yield (Scheme 3). However, in all cases we did not observe formation of 3-trifluoromethylisoxazole derivatives similar to reaction of hydroxylamine hydrochloride with 2-trifluoroacetonylisoflavones.[4]



Scheme 3. Reaction of 2-trifluoroacetonylchromones with hydroxylamine hydrochloride

To compare the behavior of 2-(3,3,3-trifluoro-2-oxopropyl)chromones **6** with 3-(2-hydroxyethyl)-2-trifluoromethylchromone derivatives (as model objects) under reaction with 1,2-bidentate nucleophiles, reactions of compounds **3** with hydrazine and hydroxylamine were carried out.

Reaction of chromone **3a** with Me_2SO_4 in acetone in the presence of base led to chemoselective methylation of 7-hydroxyl group. However, presence of electron-donating group in position 3 and electron-withdrawing CF_3 group in position 2 pursue addition of water with formation of 2-hydroxychromanone **3'b** (Scheme 4). It should be mentioned, that formation of 2-hydroxy-2-trifluoromethylchroman-4-ones is typical for the reaction of 2'-hydroxyacetophenones with ethyl trifluoroacetate under conditions of Claisen condensation.[5-8] It should be also noted that obtaining of 3-unsubstituted 2-trifluoromethylchromones requires long-time heating of 2',4-dihydroxyacetophenone with trifluoroacetic anhydride in presence of CF_3CO_2K.[9]



Scheme 4. Reaction of 2-trifluorometylchromones/chromanones **3** with hydrazine and hydroxylamine hydrochloride

Pyrazoles **9a**,**b** were obtained by refluxing of the compounds **3a**,**b** and **3'b** with hydrazine hydrate in EtOH. Reaction of the same compounds **3** with hydroxylamine hydrochloride in pyridine afford to isoxazoles **10a**,**b** and 5-trifluoromethyl-5-hydroxyisoxazoline **11**. Structure of compound **11** was confirmed by appearance of ^{13}C chemical shift (δ_C = 103.6 ppm, quartet, $^2J_{C\text{-}F}$ = 33.0 Hz) of carbon peak connected to CF_3 group.

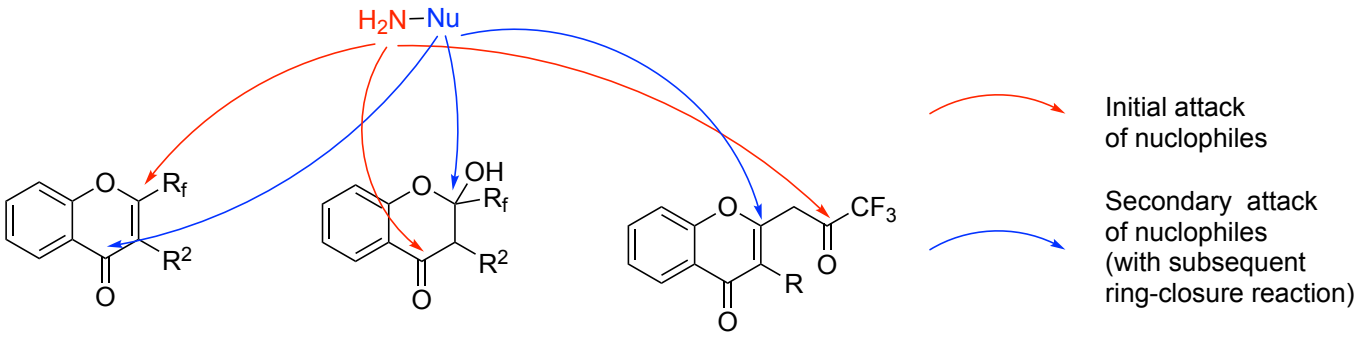


Figure 1. Direction of 1,2-bidentate nucleophile attack on trifluoromethyl derivatives of chromones/2-hydroxychroman-4-ones

It should be noted that reaction of 3-unsubstituted 2-hydroxy-2-perfluoroalkylchromanones also afforded 5-perfluoroalkyl-4,5-dihydroisoxazol-5-oles.[10] These results confirmed "conventional" reaction pathway of chromone derivatives with hydrazine[11] or hydroxylamine hydrochloride[12] in contrary to given herein reaction of 2-trifluoroacetonylchromones with hydrazine or hydroxylamine derivatives.

In general, the obtained results explain the possible interaction mechanism of chromones bearing 2-fluoroalkyl substituent with 1,2-bidentate nucleophiles: a) initial attack of hydrazine or hydroxylamine on 2-trifluoromethylchromones directed on C-2 chromone atom, subsequent attack of nucleophiles undergoes C-4 carbonyl group with formation of 3(5)-trifluoromethylpyrazoles or 3-(trifluoromethyl)isoxazoles; b) initial attack of bidentate nucleophiles more affected on C-4 atom than C-2 atom of 2-hydroxy-2-trifluoromethylchromanones; c) existence of an additional nucleophilic center in 2-(3,3,3-trifluoro-2-oxopropyl)chromones induce initial attack of 1,2-bidentate nucleophiles on exocyclic carbonyl group with possible subsequent attack on C-2 chromone atom (Figure 1).

In conclusion, the reaction of 3-substituted 2-(ar)alkylchromones with trifluoroacetic anhydride in presence of conjugative base was investigated. It was found that the synthesis of 2-(3,3,3-trifluoro-2-oxopropyl)-chromones is not limited by any substituent in position 3 of chromone ring, but reaction was not proceeded at all in the case of 2-*sec*-alkyl or 2-benzyl substituted chromones. It was stated that 2-(2-phenylethyl) substituent had no influence on trifluoroacetylation of 2-alkylchromones. On the contrary to the earlier described reaction of 2-trifluoromethyl substituted chromones/isoflavones with 1,2-bidentate nucleophiles, exocyclic carbonyl group undergoes initial nucleophilic attack, further nucleophilic attack may be directed

to C-2 chromone atom resulted in formation of 3(5)-trifluoromethylpyrazoles or 3-trifluoromethylisoxazoles.

EXPERIMENTAL

All chemicals were purchased from Enamine Ltd. and used without further purification. Column chromatography was performed using Macherey-Nagel Silica 60, 0.04-0.063 mm silica gel. All reactions were monitored by TLC on Macherey-Nagel ALUGRAM® Xtra SIL G/UV_{254} plates.

^{1}H, ^{13}C, ^{19}F, and 2D NMR spectra were recorded on Varian 500 (500/125/470 MHz), Varian 400 (400/100/376 MHz) or Agilent propulse 600 (600/150/564 MHz) spectrometers in $CDCl_3$ [residual $CHCl_3$ (δ_H = 7.26 ppm) or $CDCl_3$ (δ_C = 77.16 ppm)] or DMSO-d_6 [residual $SO(CD_3)(CD_2H)$ (δ_H = 2.50 ppm) or $SO(CD_3)_2$ or $SO(CD_3)_2$ (δ_C = 39.52 ppm) as internal standard]. ^{19}F NMR spectra were recorded using $CFCl_3$ (δ_C = 0.00 ppm) as external standard]. Melting points were determined in open capillary tubes using Büchi B-535 apparatus. Mass spectra were obtained using an Agilent 1100 spectrometer using APCI (atmospheric-pressure chemical ionization). Elemental analysis was performed on a vario MICRO cube automated CHNS-analyzer.

*General procedure for the synthesis of ketones **2a-d**.*

A solution of 55 mmol resorcinol (**1a**) or 4-methoxyresorcinol (**1b**), 50 mmol of the appropriate acetonitrile in 25 mL of boron trifluoride etherate at stirring was saturated with anhydrous HCl gas over a 6 h period at ambient temperature. Then, the reaction mixture was carefully poured into 500 mL of water at 80 °C and heated to reflux for 2 h. The resulted solid formed at cooling was filtered off and crystallized from the MeOH-H_2O (1:1) mixture to afford **2a-d**.

1-(2,4-Dihydroxyphenyl)-2-methoxyethan-1-one (2a). Yield 4.83 g (53%); off-white powder; mp 139 – 141 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.93 (s, 1H), 10.60 (s, 1H), 7.67 (d, J = 8.8 Hz, 1H), 6.40 – 6.32 (m, 1H), 6.31 – 6.25 (m, 1H), 4.65 (s, 2H), 3.35 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 199.3, 164.7, 163.6, 132.0, 111.7, 108.3, 102.6, 74.3, 58.6; MS (APCI) *m/z*: 181.0 ($[M-H]^-$, 100). Anal. Calcd for $C_9H_{10}O_4$: C, 59.34; H, 5.53. Found: C, 59.47; H, 5.35.

1-(2,4-Dihydroxy-5-methoxyphenyl)-2-methoxyethan-1-one (2b). Yield 4.88 g (46%); off-white powder; mp 101 – 103 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.18 (s, 1H), 6.34 (s, 1H), 4.66 (s, 2H), 3.74 (s, 3H), 3.35 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 198.1, 158.0, 155.7, 141.4, 111.6, 109.8, 103.3, 74.8, 58.5, 56.2; MS (APCI) *m/z*: 211.0 ($[M-H]^-$, 100). Anal. Calcd for $C_{10}H_{12}O_5$: C, 56.60; H, 5.70. Found: C, 56.71; H, 5.49.

1-(2,4-Dihydroxyphenyl)-2-(4-methoxyphenoxy)ethan-1-one (2c). Yield 8.92 g (65%); off-white powder; mp 177 – 179 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.77 (s, 1H), 10.65 (s, 1H), 7.79 (d, J = 8.8 Hz, 1H), 6.90 – 6.79 (m, 4H), 6.39 (dd, J = 8.8, 2.3 Hz, 1H), 6.32 (d, J = 2.3 Hz, 1H), 5.32 (s, 2H), 3.68 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 197.0, 164.9, 163.4, 153.6, 152.1, 132.1, 115.5, 114.6, 111.8, 108.4, 102.6, 70.5, 55.4; MS (APCI) *m/z*: 275.0 ([M+H]$^+$, 100); 273.0 ([M-H]$^-$, 100). Anal. Calcd for $C_{15}H_{14}O_5$: C, 65.69; H, 5.15. Found: C, 65.89; H, 5.03.

4-Chloro-1-(2,4-dihydroxyphenyl)butan-1-one (2d). Yield 6.76 g (63%); off-white powder; mp 119 – 121 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.68 (s, 1H), 10.63 (s, 1H), 7.76 (d, J = 8.9 Hz, 1H), 6.37 (dd, J = 8.8, 2.2 Hz, 1H), 6.25 (d, J = 2.2 Hz, 1H), 3.45 (t, J = 6.4 Hz, 2H), 2.95 (t, J = 7.3 Hz, 2H), 1.83 – 1.65 (m, 2H); ^{13}C NMR (150 MHz, DMSO-d_6): δ 204.9, 164.8, 164.4, 132.9, 112.6, 108.2, 102.5, 60.2, 34.1, 27.7; MS (APCI) *m/z*: 215.0 ([M+H]$^+$, 100); 213.0 ([M-H]$^-$, 100). Anal. Calcd for $C_{10}H_{11}ClO_3$: C, 55.96; H, 5.17. Found: C, 55.73; H, 5.36.

7-Hydroxy-3-(2-hydroxyethyl)-2-(trifluoromethyl)-4*H*-chromen-4-one (3a). Trifluoroacetic anhydride (2.25 mL, 15 mmol) was added to cooled solution of 910 mg (5 mmol) of ketone **2c** in 10 mL of pyridine at stirring. Reaction mixture was kept at rt for 5 days then diluted with 200 mL 3N chilled HCl. Formed precipitate was filtered off, dried at air, and crystallized from MeOH to afford **3a**. Yield 645 mg (47%); off-white powder; mp 228 – 230 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.06 (s, 1H), 7.90 (d, J = 8.8 Hz, 1H), 7.02 – 6.92 (m, 1H), 6.84 (s, 1H), 4.76 (s, 1H), 3.54 – 3.43 (m, 2H), 2.80 – 2.67 (m, 2H); ^{13}C NMR (150 MHz, DMSO-d_6): δ 175.5, 163.7, 156.3, 147.1 (q, J_{C-F} = 35.9 Hz), 127.2, 121.0, 119.79 (q, J_{C-F} = 275.9 Hz), 116.2, 114.8, 101.9, 59.1, 27.0; ^{19}F NMR (470 MHz, DMSO-d_6): δ -63.7; MS (APCI) *m/z*: 275.0 ([M+H]$^+$, 100); 273.0 ([M-H]$^-$, 100). Anal. Calcd for $C_{12}H_9F_3O_4$: C, 52.57; H, 3.31. Found: C, 52.33; H, 3.47.

*Methylation of 7-hydroxy-2-trifluoromethylchromones **3a**.* To a stirred solution of 1.37 g (5 mmol) of chromone **3a** in 25 mL acetone was added 2.07 g (15 mmol) K_2CO_3 and 0.57 mL (6 mmol) Me_2SO_4. Reaction mixture was stirred at reflux for 4 h, and solid formed was filtered off. The resulted solution was evaporated to dryness at reduced pressure, diluted with 50 mL water and acidified with 1 N HCl to pH 4. The formed precipitate (mixture of compounds **3b** and **3'b**) was filtered off and dried at air. The formed compounds were separated by column chromatography using CH_2Cl_2-MeOH 50:1 mixture as eluent to afford methoxy derivatives **3b** and **3'b**.

3-(2-Hydroxyethyl)-7-methoxy-2-(trifluoromethyl)-4*H*-chromen-4-one (3b). Yield 1110 mg (77%); off-white powder; mp 124 – 126 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.91 (d, J = 8.9 Hz, 1H), 7.12 (d, J = 2.4 Hz, 1H), 7.05 (dd, J = 8.9, 2.4 Hz, 1H), 4.77 (t, J = 5.8 Hz, 1H), 3.89 (s, 3H), 3.57 – 3.42 (m, 2H), 2.82 – 2.66 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 175.6, 164.6, 156.4, 147.3 (q, J_{C-F} =36.1 Hz),

126.7, 121.3, 119.7 (q, J_{C-F} = 276.0 Hz), 115.9, 115.7, 100.2, 59.1, 56.3, 26.9; ^{19}F NMR (470 MHz, DMSO-d_6): δ -63.8; MS (APCI) *m/z*: 289.0 ([M+H]$^+$, 100). Anal. Calcd for $C_{13}H_{11}F_3O_4$: C, 54.17; H, 3.85. Found: C, 54.09; H, 3.70.

2-Hydroxy-3-(2-hydroxyethyl)-7-methoxy-2-(trifluoromethyl)-2,3-dihydro-4*H*-chromen-4-one (3b'). Yield 184 mg (12%); off-white powder; mp 100 – 102 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.74 (d, *J* = 8.8 Hz, 1H), 6.78 (d, *J* = 2.4 Hz, 1H), 6.71 (d, *J* = 2.4 Hz, 1H), 4.30 – 4.08 (m, 2H), 3.86 (s, 3H), 3.54 (t, *J* = 9.1 Hz, 1H), 2.71 – 2.56 (m, 1H), 2.36 – 2.16 (m, 1H); ^{13}C NMR (150 MHz, DMSO-d_6): δ 188.1, 167.2, 159.3, 128.7, 122.4 (q, J_{C-F} = 286.2 Hz), 112.0, 110.9, 106.3 (q, J_{C-F} = 33.5 Hz), 101.4, 70.1, 56.5, 48.4, 30.1; ^{19}F NMR (376 MHz, DMSO-d_6): δ -81.6; MS (APCI) *m/z*: 289.0 [M-H_2O+H]$^+$. Anal. Calcd for $C_{13}H_{13}F_3O_5$: C, 50.99; H, 4.28. Found: C, 50.83; H, 4.49.

*General procedure for the synthesis of 2-methylchromones **4d** and **5a-c**.*

A mixture of 10 mmol of corresponding ketone **2** and 980 mg (5 mmol) of AcOK in 10 mL of acetic anhydride was stirred at 130 – 140 °C for 8 h. A reaction mixture was poured into 250 mL of ice-water and formed solid was filtered off to afford intermediate hydroxylated isoflavone acetates which were used for the next step without purification (except compound **4d**). Acetates were dissolved in 25 mL EtOH containing 2 mL of conc. H_2SO_4, stirred under reflux for 6 h and poured into 100 mL of water. The formed precipitates were filtered off and crystallized from MeOH. Compound **4d** was purified by column chromatography using EtOAc–hexanes 1:1 mixture as eluent.

2-(7-Acetoxy-2-methyl-4-oxo-4*H*-chromen-3-yl)ethyl acetate (4d). Yield 1.70 g (56%); off-white powder; mp 80 – 82 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.15 (d, *J* = 8.7 Hz, 1H,) 7.20 – 7.15 (m, 1H), 7.11 – 7.02 (m, 1H), 4.19 (t, *J* = 6.7 Hz, 2H), 2.85 (t, *J* = 6.7 Hz, 2H), 2.42 (s, 3H), 2.31 (s, 3H), 2.00 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 176.6, 170.9, 168.6, 164.0, 156.3, 154.2, 127.2, 120.6, 119.0, 117.4, 110.6, 62.8, 24.6, 21.2, 21.0, 18.4; MS (APCI) *m/z*: 305.0 ([M+H]$^+$, 100); 303.0 ([M-H]$^-$, 100). Anal. Calcd for $C_{16}H_{16}O_6$: C, 63.15; H, 5.30. Found: C, 63.03; H, 5.48.

7-Hydroxy-3-methoxy-2-methyl-4*H*-chromen-4-one (5a). Yield 1.32 g (64%); off-white powder; mp 214 – 216 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.70 (s, 1H), 7.86 (d, *J* = 8.7 Hz, 1H), 6.87 (dd, *J* = 8.7, 2.3 Hz, 1H), 6.78 (d, *J* = 2.3 Hz, 1H), 3.73 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 172.1, 162.3, 158.5, 156.6, 140.1, 126.7, 116.7, 114.7, 102.0, 59.8, 15.0; MS (APCI) *m/z*: 207.0 ([M+H]$^+$, 100); 205.0 ([M-H]$^-$, 100). Anal. Calcd for $C_{11}H_{10}O_4$: C, 64.08; H, 4.89. Found: C, 64.23; H, 5.06.

7-Hydroxy-3,6-dimethoxy-2-methyl-4*H*-chromen-4-one (5b). Yield 1.72 g (73%); off-white powder; mp 196 – 198 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.48 (s, 1H), 7.30 (s, 1H), 6.83 (s, 1H), 3.85 (s, 3H), 3.72 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6): δ 171.7, 157.9, 152.5, 150.8, 146.5, 139.8,

116.2, 104.1, 102.7, 59.7, 55.8, 14.9; MS (APCI) *m/z*: 237.2 ([M+H]$^+$, 100); 235.2 ([M-H]$^-$, 100). Anal. Calcd for $C_{12}H_{12}O_5$: C, 61.02; H, 5.12. Found: C, 60.89; H, 5.03.

7-Hydroxy-3-(4-methoxyphenoxy)-2-methyl-4*H*-chromen-4-one (5c). Yield 2.60 g (87%); off-white powder; mp 215 – 217 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.82 (s, 1H), 7.85 (d, J = 8.7 Hz, 1H), 6.91 (dd, J = 8.7, 1.8 Hz, 1H), 6.89 – 6.79 (m, 5H), 3.68 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 171.2, 162.6, 159.9, 156.9, 154.4, 151.2, 135.7, 126.8, 116.5, 115.6, 114.9, 114.6, 102.2, 55.4, 15.3; MS (APCI) *m/z*: 299.0 ([M+H]$^+$, 100); 297.0 ([M-H]$^-$, 100). Anal. Calcd for $C_{17}H_{14}O_5$: C, 68.45; H, 4.73. Found: C, 68.28; H, 4.62.

2-(7-Hydroxy-2-methyl-4-oxo-4*H*-chromen-3-yl)ethyl acetate (5e). The diacetate **4d** (5 mmol) was dissolved in 15 mL EtOH and 5 mL of 1 N NaOH was added, stirred at ambient temperature for 15 min and the final reaction mixture was acidified with 1 N HCl to pH 3, diluted with 100 mL of water, the solid formed was filtered off, crystallized from MeOH-H_2O (1:1) mixture to afford **5e**. Yield 957 mg (73%); off-white powder; mp 209 – 211 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.68 (s, 1H), 7.83 (d, J = 8.7 Hz, 1H), 6.86 (dd, J = 8.7, 2.0 Hz, 1H), 6.75 (d, J = 2.0 Hz, 1H), 4.07 (t, J = 6.7 Hz, 2H), 2.73 (t, J = 6.7 Hz, 2H), 2.39 (s, 3H), 1.98 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 175.5, 170.3, 163.1, 162.3, 157.1, 126.8, 115.7, 114.9, 114.7, 101.8, 62.2, 24.0, 20.7, 18.0; MS (APCI) *m/z*: 263.0 ([M+H]$^+$, 100); 261.0 ([M-H]$^-$, 100). Anal. Calcd for $C_{14}H_{14}O_5$: C, 64.12; H, 5.38. Found: C, 64.29; H, 5.28.

7-Hydroxy-3-(2-methoxyethyl)-2-methyl-4*H*-chromen-4-one (5f). The solution of diacetate **4d** (5 mmol) was refluxed in mixture of MeOH (20 mL) and 37% HCl (5 mL) for 8 h, cooled to ambient temperature, diluted with 100 mL water, precipitate formed was filtered off and crystallized from MeOH-H_2O (1:1) mixture to afford **5f**. Yield 668 mg (57%); off-white powder; mp 178 – 180 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.65 (s, 1H), 7.83 (d, J = 8.7 Hz, 1H), 6.85 (dd, J = 8.7, 1.7 Hz, 1H), 6.74 (d, J = 1.7 Hz, 1H), 3.36 (t, J = 6.8 Hz, 2H), 3.21 (s, 3H), 2.65 (t, J = 6.8 Hz, 2H), 2.36 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6): δ 175.5, 162.8, 162.2, 157.1, 126.8, 116.5, 115.0, 114.6, 101.8, 70.4, 57.9, 24.7, 18.1; MS (APCI) *m/z*: 235.2 ([M+H]$^+$, 100); 233.1 ([M-H]$^-$, 100). Anal. Calcd for $C_{13}H_{14}O_4$: C, 66.66; H, 6.02. Found: C, 66.51; H, 6.15.

*General procedure for the synthesis of 7-hydroxy-2-benzyl/phenethyl chromones **5g**,**h**.*

To a stirred solution of 1.82 g (10 mmol) of ketone **2a** in 50 mL acetone, 6.90 g (50 mmol) K_2CO_3 and 40 mmol 4-methoxyphenylacetyl chloride or *3*-(4-methoxyphenyl)propionyl chloride were added. The reaction mixture was stirred under inert atmosphere at reflux for 20 h, and formed solid was filtered off. The solution was evaporated to dryness under reduced pressure, diluted with 100 mL 4 N HCl and refluxed for 1 h. The resulted residue was filtered off, washed with saturated aqueous $NaHCO_3$ solution and crystallized from MeOH to afford **5g** or **5h**.

7-Hydroxy-3-methoxy-2-(4-methoxybenzyl)-4*H*-chromen-4-one (5g). Yield 1.69 g (54%); off-white powder; mp 227 – 229 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.45 (s, 1H), 7.70 (d, J = 8.8 Hz, 1H), 7.24 (d, J = 8.4 Hz, 2H), 7.00 (d, J = 8.4 Hz, 2H), 6.89 – 6.78 (m, 1H), 6.78 – 6.70 (m, 1H), 4.33 (s, 2H), 3.81 (s, 3H), 3.21 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 160.7, 160.7, 159.0, 154.2, 145.2, 131.5, 127.9, 125.8, 124.0, 113.4, 113.1, 111.2, 101.9, 67.9, 58.0, 55.1; MS (APCI) *m/z*: 312.2 ([M+H]$^+$, 100); 311.2 ([M-H]$^-$, 100). Anal. Calcd for $C_{18}H_{16}O_5$: C, 69.22; H, 5.16. Found: C, 69.11; H, 5.02.

7-Hydroxy-3-methoxy-2-(4-methoxyphenethyl)-4*H*-chromen-4-one (5h). Yield 1.40 g (43%); off-white powder; mp 175 – 177 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.73 (s, 1H), 7.86 (d, J = 8.8 Hz, 1H), 7.12 (d, J = 8.5 Hz, 2H), 6.88 (dd, J = 8.8, 2.0 Hz, 1H), 6.85 – 6.78 (m, 3H), 3.69 (s, 3H), 3.53 (s, 3H), 3.02 – 2.86 (m, 4H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 172.1, 162.3, 160.2, 157.7, 156.6, 140.1, 132.1, 129.3, 126.6, 116.5, 114.7, 113.7, 101.9, 59.8, 54.9, 31.3, 30.3; MS (APCI) *m/z*: 327.1 ([M+H]$^+$, 100); 325.0 ([M-H]$^-$, 100). Anal. Calcd for $C_{19}H_{18}O_5$: C, 69.93; H, 5.56. Found: C, 69.72; H, 5.69.

*General procedure for the synthesis 3,3,3-trifluoroacetonyl chromones **6**.*

A mixture of 2 mmol of appropriate 2-substituted chromone **5**, 304 mg (2 mmol) of potassium trifluoroacetate in 3 mL of trifluoroacetic anhydride was stirred under reflux for 16 - 24 h. The reaction mixture was poured into 100 mL of chilled water and the formed precipitate was filtered off to afford **6**. These compounds were purified by column chromatography using benzene-acetone mixture (2:1) as eluent. Then, these compounds were dissolved in 2 mL of acetone and treated with water, stirred for 16 h at ambient temperature and the *gem*-diols of **6** formed were filtered off and dried at air.

7-Hydroxy-3-methoxy-2-(3,3,3-trifluoro-2,2-dihydroxypropyl)-4*H*-chromen-4-one (6a). Yield 461 mg (72%); off-white powder; mp 193 – 195 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.73 (s, 1H), 7.88 (d, J = 8.9 Hz, 1H), 7.21 (s, 2H), 6.88 (d, J = 8.9 Hz, 1H), 6.78 (s, 1H), 3.77 (s, 3H), 3.14 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 172.6, 162.5, 156.9, 155.4, 142.1, 126.8, 123.8 (d, J_{C-F} = 289.7 Hz), 116.9, 114.9, 102.2, 92.6 (q, J_{C-F} = 31.2 Hz), 60.0, 35.3; ^{19}F NMR (376 MHz, DMSO-d_6): δ -84.3; MS (APCI) *m/z*: 321.0 ([M+H]$^+$, 100); 319.0 ([M-H]$^-$, 100). Anal. Calcd for $C_{13}H_{11}F_3O_6$: C, 48.76; H, 3.46. Found: C, 48.92; H, 3.27.

7-Hydroxy-3,6-dimethoxy-2-(3,3,3-trifluoro-2,2-dihydroxypropyl)-4*H*-chromen-4-one (6b). Yield 399 mg (57%); off-white powder; mp 141 – 143 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.60 (s, 1H), 7.33 (s, 1H), 7.21 (s, 2H), 6.87 (s, 1H), 3.86 (s, 3H), 3.77 (s, 3H), 3.14 (s, 2H); ^{13}C NMR (150 MHz, DMSO-d_6): δ 172.1, 154.8, 152.8, 151.2, 146.7, 141.7, 123.7 (q, J_{C-F} = 289.5 Hz), 116.4, 104.1, 102.9, 92.5 (q, J_{C-F} = 30.6 Hz), 59.8, 55.8, 35.2; ^{19}F NMR (470 MHz, DMSO-d_6): δ -83.7; MS (APCI) *m/z*: 351.0 ([M+H]$^+$, 100); 249.0 ([M-H]$^-$, 100). Anal. Calcd for $C_{14}H_{13}F_3O_7$: C, 48.01; H, 3.74. Found: C, 48.12; H, 3.91.

7-Hydroxy-3-(4-methoxyphenoxy)-2-(3,3,3-trifluoro-2,2-dihydroxypropyl)-4*H*-chromen-4-one (6c). Yield 528 mg (64%); off-white powder; mp 192 – 194 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.83 (s, 1H), 7.83 (d, J = 8.6 Hz, 1H), 7.26 (s, 2H), 6.95 – 6.71 (m, 6H), 3.65 (s, 3H), 3.12 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 171.4, 162.8, 157.1, 156.7, 154.5, 151.3, 137.8, 126.9, 123.6 (q, J_{C-F} = 289.9 Hz), 116.7, 116.2, 115.1, 114.5, 102.4, 92.7 (q, J_{C-F} = 30.7 Hz), 55.5, 35.6; ^{19}F NMR (376 MHz, DMSO-d_6): δ -83.9; MS (APCI) *m/z*: 413.2 ([M+H]$^+$, 100); 393.0 ([M-H_2O-H]$^-$, 100). Anal. Calcd for $C_{19}H_{15}F_3O_7$: C, 55.35; H, 3.67. Found: C, 55.58; H, 3.82.

2-(7-Hydroxy-4-oxo-2-(3,3,3-trifluoro-2,2-dihydroxypropyl)-4*H*-chromen-3-yl)ethyl acetate (6e). Yield 421 mg (56%); off-white powder; mp 190 – 192 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.69 (s, 1H), 7.86 (d, J = 8.6 Hz, 1H), 7.26 (s, 2H), 6.92 – 6.83 (m, 1H), 6.78 – 6.72 (m, 1H), 4.15 – 4.04 (m, 2H), 3.13 (s, 2H), 2.90 – 2.75 (m, 2H), 1.98 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 176.0, 170.3, 162.4, 159.9, 157.3, 126.8, 123.6 (q, J_{C-F} = 290.6 Hz), 119.0, 115.1, 114.9, 92.8 (q, J_{C-F} = 30.4 Hz), 62.3, 38.1, 24.3, 20.7; ^{19}F NMR (470 MHz, DMSO-d_6): δ -83.8; MS (APCI) *m/z*: 377.2 ([M+H]$^+$, 100); 375.0 ([M-H]$^-$, 38), 357.0 ([M-H_2O-H]$^-$, 100). Anal. Calcd for $C_{16}H_{15}F_3O_7$: C, 51.07; H, 4.02. Found: C, 50.89; H, 4.17.

7-Hydroxy-3-(2-methoxyethyl)-2-(3,3,3-trifluoro-2,2-dihydroxypropyl)-4*H*-chromen-4-one (6f). Yield 515 mg (74%); off-white powder; mp 163 – 165 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.66 (s, 1H), 7.85 (d, J = 7.9 Hz, 1H), 7.22 (s, 2H), 6.92 – 6.82 (m, 1H), 6.78 – 6.72 (m, 1H), 3.53 – 3.32 (m, 2H), 3.22 (s, 3H), 3.13 (s, 2H), 2.82 – 2.66 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 176.1, 162.3, 159.5, 157.3, 126.8, 123.7 (q, J_{C-F} = 289.7 Hz), 119.9, 115.2, 114.8, 101.9, 92.8 (q, J_{C-F} = 30.9 Hz), 70.5, 58.0, 38.9 (d, J_{C-F} = 187.7 Hz), 25.0; ^{19}F NMR (470 MHz, DMSO-d_6): δ -83.8; MS (APCI) *m/z*: 349.0 ([M+H]$^+$, 100); 347.0 ([M-H]$^-$, 63), 329.0 ([M-H_2O-H]$^-$, 100). Anal. Calcd for $C_{15}H_{15}F_3O_6$: C, 51.73; H, 4.34. Found: C, 51.87; H, 4.45.

7-Hydroxy-3-methoxy-2-[3,3,3-trifluoro-2,2-dihydroxy-1-(4-methoxybenzyl)propyl]-4*H*-chromen-4-one (6h). Yield 607 mg (69%); off-white powder; mp 109 – 110 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.77 (s, 1H), 7.80 (d, J = 8.6 Hz, 1H), 7.29 (s, 1H), 7.25 (s, 1H), 6.93 (d, J = 8.6 Hz, 2H), 6.91 – 6.85 (m, 2H), 6.71 (d, J = 8.6 Hz, 2H), 3.85 – 3.74 (m, 1H), 3.61 (s, 3H), 3.22 (s, 3H), 3.21 – 3.08 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 171.9, 162.3, 157.7, 157.0, 156.4, 141.9, 130.5, 129.6, 126.5, 123.7 (q, J_{C-F} = 290.1 Hz), 116.4, 114.7, 113.7, 102.1, 93.6 (q, J_{C-F} = 30.1 Hz), 59.1, 54.9, 46.0, 30.8; ^{19}F NMR (470 MHz, DMSO-d_6): δ -81.9; MS (APCI) *m/z*: 441.0 ([M+H]$^+$, 100); 439.0 ([M-H]$^-$, 87), 421.0 ([M-H_2O-H]$^-$, 100). Anal. Calcd for $C_{21}H_{19}F_3O_7$: C, 57.28; H, 4.35. Found: C, 57.01; H, 4.32.

General procedure for the synthesis of 3-trifluoromethylpyrazoles 7.

A mixture of 1 mmol of appropriate 2-(3,3,3-trifluoroacetonyl)chromone **6** and 210 mg (2 mmol) hydrazine dihydrochloride in 5 mL of anhydrous EtOH was refluxed for 16 h. The reaction mixture was concentrated

under reduced pressure, diluted with 20 mL of water and neutralized with saturated aqueous solution of $NaHCO_3$. The residue formed was filtered off, dried at air and purified by column chromatography using CH_2Cl_2-MeOH 50:1 mixture as an eluent to afford **7**.

1-(2,4-Dihydroxyphenyl)-4-methoxy-2-(5-(trifluoromethyl)-1*H*-pyrazol-3-yl)butan-1-one (7f). Yield 224 mg (65%); off-white powder; mp 160 – 162 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.62 (s, 1H), 12.28 (s, 1H), 10.77 (s, 1H), 7.91 (d, J = 8.9 Hz, 1H), 6.60 (s, 1H), 6.41 (d, J = 8.9 Hz, 1H), 6.29 (s, 1H), 5.09 (t, J = 7.3 Hz, 1H), 3.30 – 3.22 (m, 2H), 3.16 (s, 3H), 2.36 – 2.23 (m, 1H), 2.16 – 2.02 (m, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 200.7, 165.4, 164.7, 142.6, 141.0 (q, J_{C-F} = 36.8 Hz), 132.9, 121.7 (q, J_{C-F} = 268.2 Hz), 111.8, 108.6, 102.7, 102.5, 69.2, 57.9, 39.9, 31.9; ^{19}F NMR (470 MHz, DMSO-d_6): δ -60.4; MS (APCI) *m/z*: 345.2 ([M+H]$^+$, 100); 343.2 ([M-H]$^-$, 100). Anal. Calcd for $C_{15}H_{15}F_3N_2O_4$: C, 52.33; H, 4.39; N, 8.14. Found: C, 52.18; H, 4.18; N, 8.27.

1-(2-Hydroxyphenyl)-2-[5-(trifluoromethyl)-1*H*-pyrazol-3-yl]propan-1-one (7i). Yield 230 mg (81%); brown oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.01 (s, 1H), 7.81 (d, J = 8.1 Hz, 1H), 7.54 (t, J = 7.6 Hz, 1H), 7.03 (d, J = 8.4 Hz, 1H), 6.95 (t, J = 7.7 Hz, 1H), 6.48 (s, 1H), 5.03 (q, J = 7.2 Hz, 1H), 1.66 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.7, 163.6, 144.0, 142.7 (q, J_{C-F} = 38.2 Hz), 137.6, 129.9, 121.3 (q, J_{C-F} = 268.6 Hz), 119.6, 119.2, 117.7, 103.1, 38.2, 19.7; ^{19}F NMR (376 MHz, $CDCl_3$): δ -62.1; MS (APCI) *m/z*: 285.2 ([M+H]$^+$, 100); 283.0 ([M-H]$^-$, 100). Anal. Calcd for $C_{13}H_{11}F_3N_2O_2$: C, 54.93; H, 3.90; N, 9.86. Found: C, 55.16; H, 3.76; N, 10.01.

1-(2,4-Dihydroxyphenyl)-2-[5-(trifluoromethyl)-1*H*-pyrazol-3-yl]propan-1-one (7j). Yield 246 mg (82%); off-white powder; mp 219 – 221 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.55 (s, 1H), 12.32 (s, 1H), 10.76 (s, 1H), 7.92 (d, J = 8.9 Hz, 1H), 6.56 (s, 1H), 6.43 (dd, J = 8.8, 2.4 Hz, 1H), 6.32 (d, J = 2.4 Hz, 1H), 5.08 (q, J = 7.0 Hz, 1H), 1.51 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 202.3, 165.8, 165.3, 144.7, 141.4 (q, J_{C-F} = 38.2 Hz), 133.5, 122.24 (q, J_{C-F} = 268.3 Hz), 111.7, 109.0, 103.2, 102.6, 38.1, 18.0; ^{19}F NMR (376 MHz, DMSO-d_6) δ -60.9; MS (APCI) *m/z*: 301.2 ([M+H]$^+$, 100); 299.0 ([M-H]$^-$, 100). Anal. Calcd for $C_{13}H_{11}F_3N_2O_3$: C, 52.01; H, 3.69; N, 9.33. Found: C, 51.81; H, 3.55; N, 9.45.

*General procedure for the synthesis of oximes **8**.*

A mixture of 1 mmol of appropriate 2-(3,3,3-trifluoroacetonyl)chromone **6** and 150 mg (2 mmol) hydroxylamine hydrochloride in 5 mL of anhydrous EtOH was refluxed for 16 h. The reaction mixture was concentrated under reduced pressure, diluted with 20 mL of water and neutralized with saturated aqueous solution of $NaHCO_3$. A formed precipitate was filtered off, dried at air and purified by column chromatography in CH_2Cl_2-MeOH mixture (50:1) as an eluent.

7-Hydroxy-3-methoxy-2-[(2*Z*)-3,3,3-trifluoro-2-(hydroxyimino)propyl]-4*H*-chromen-4-one (8a). Yield 276 mg (87%); off-white powder; mp 189 – 191 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.88 (s, 1H), 10.80 (s, 1H), 7.88 (d, J = 8.8 Hz, 1H), 6.89 (dd, J = 8.8, 2.1 Hz, 1H), 6.70 (d, J = 2.1 Hz, 1H), 4.00 (s, 2H), 3.77 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 172.2, 162.7, 156.5, 154.2, 142.3 (q, $J_{C\text{-}F}$ = 31.8 Hz), 140.3, 126.9, 121.1 (q, $J_{C\text{-}F}$ = 273.4 Hz), 116.6, 115.1, 101.8, 59.6, 24.0; ^{19}F NMR (470 MHz, DMSO-d_6): δ -67.1; MS (APCI) *m/z*: 318.0 ([M+H]$^+$, 100); 316.0 ([M-H]$^-$, 100). Anal. Calcd for $C_{13}H_{10}F_3NO_5$: C, 49.22; H, 3.18; N, 4.42. Found: C, 49.49; H, 2.94; N, 4.65.

7-Hydroxy-3-(4-methoxyphenoxy)-2-(3,3,3-trifluoro-2-(hydroxyimino)propyl)-4*H*-chromen-4-one (8c). Yield 348 mg (85%); off-white powder; mp 224 – 226 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.88 (s, 1H), 10.88 (s, 1H), 7.85 (d, J = 8.7 Hz, 1H), 6.98 – 6.75 (m, 6H), 3.99 (s, 2H), 3.70 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 171.0, 162.9, 156.7, 155.6, 154.5, 150.7, 141.6 (q, $J_{C\text{-}F}$ = 32.0 Hz), 136.0, 127.0, 120.9 (q, $J_{C\text{-}F}$ = 273.5 Hz), 116.4, 115.9, 115.3, 114.4, 102.0, 55.4, 24.3; ^{19}F NMR (470 MHz, DMSO-d_6): δ -67.0; MS (APCI) *m/z*: 410.2 ([M+H]$^+$, 100); 408.0 ([M-H]$^-$, 100). Anal. Calcd for $C_{19}H_{14}F_3NO_6$: C, 55.75; H, 3.45; N, 3.42. Found: C, 55.58; H, 3.58; N, 3.60.

7-Hydroxy-3-methoxy-2-[(2Z)-3,3,3-trifluoro-2-(hydroxyimino)-1-(4-methoxybenzyl)propyl]-4*H*-chromen-4-one (8h). Yield 244 mg (56%); off-white powder; mp 228 – 229 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 112.98 (s, 1H), 10.87 (s, 1H), 7.86 (d, J = 8.6 Hz, 1H), 7.15 (d, J = 8.5 Hz, 2H), 6.96 – 6.89 (m, 2H), 6.81 (d, J = 8.5 Hz, 2H), 5.09 (dd, J = 9.9, 6.0 Hz, 1H), 3.66 (s, 3H), 3.52 (s, 3H), 3.36 – 3.31 (m, 1H), 3.13 (dd, J = 13.6, 6.0 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 172.0, 162.7, 158.1, 156.4, 155.0, 144.8 (q, $J_{C\text{-}F}$ = 30.6 Hz), 140.9, 129.8, 129.6, 126.8, 121.2 (q, $J_{C\text{-}F}$ = 275.0 Hz), 116.4, 115.2, 113.8, 101.9, 59.4, 54.9, 37.2, 32.3; ^{19}F NMR (470 MHz, DMSO-d_6): δ -64.4; MS (APCI) *m/z*: 438.0 ([M+H]$^+$, 100); 436.0 ([M-H]$^-$, 100). Anal. Calcd for $C_{21}H_{18}F_3NO_6$: C, 57.67; H, 4.15; N, 3.20. Found: C, 57.91; H, 3.89; N, 3.03.

*General procedure for the synthesis of pyrazoles **9a**,**b**.*

A solution of 1 mmol of corresponding 2-trifluoromethyl derivative **3a**,**b** or **3'b** and 0.2 mL of hydrazine hydrate in 5 mL of EtOH was refluxed for 2 h. The reaction mixture was diluted with 50 mL water, neutralized with 0.1 N HCl, the formed precipitate was filtered off, dried at air, and purified by column chromatography using CH_2Cl_2-MeOH mixture (20:1) as eluent to afford **9a**,**b**.

4-(4-(2-Hydroxyethyl)-5-(trifluoromethyl)-1*H*-pyrazol-3-yl)benzene-1,3-diol (9a). Yield 216 mg (75%); off-white powder; mp 198 – 200 °C; ^{1}H NMR (600 MHz, DMSO-d_6): δ 13.17 (s, 1H), 9.69 (s, 1H), 9.56 (s, 1H), 7.04 (d, J = 8.3 Hz, 1H), 6.44 (d, J = 2.1 Hz, 1H), 6.32 (dd, J = 8.3, 2.1 Hz, 1H), 4.66 (t, J = 5.1 Hz, 1H), 3.40 – 3.31 (m, 2H), 2.61 (t, J = 7.8 Hz, 2H); ^{13}C NMR (150 MHz, DMSO-d_6): δ 159.5, 156.6, 140.4, 139.0 (q, $J_{C\text{-}F}$ = 34.6 Hz), 131.9, 122.8 (q, $J_{C\text{-}F}$ = 268.8 Hz), 113.2, 106.9, 102.9, 61.4, 26.9; ^{19}F NMR

(470 MHz, DMSO-d_6): δ -59.1; MS (APCI) *m/z*: 289.0 ([M+H]$^+$, 100); 287.0 ([M-H]$^-$, 100). Anal. Calcd for $C_{12}H_{11}F_3N_2O_3$: C, 50.01; H, 3.85; N, 9.72. Found: C, 50.18; H, 3.98; N, 9.81.

2-(4-(2-Hydroxyethyl)-5-(trifluoromethyl)-1*H*-pyrazol-3-yl)-5-methoxyphenol (9b). Yield 254 mg (84%); off-white powder; mp 175 – 177 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.24 (s, 1H), 9.87 (s, 1H), 7.19 (d, J = 8.3 Hz, 1H), 6.59 – 6.47 (m, 2H), 4.62 (s, 1H), 3.76 (s, 3H), 3.45 – 3.34 (m, 2H), 2.68 – 2.57 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 161.2, 156.6, 140.0, 139.0 (q, J_{C-F} = 34.8 Hz), 131.9, 122.8 (q, J_{C-F} = 267.4 Hz), 113.5, 108.6, 105.0, 101.6, 61.3, 55.1, 26.9; ^{19}F NMR (470 MHz, DMSO-d_6): δ -59.2; MS (APCI) *m/z*: 303.2 ([M+H]$^+$, 100); 301.2 ([M-H]$^-$, 100). Anal. Calcd for $C_{13}H_{13}F_3N_2O_3$: C, 51.66; H, 4.34; N, 9.27. Found: C, 51.55; H, 4.17; N, 9.13.

*General procedure for the synthesis of isoxazole derivatives **10** and **11.***

A solution of 1 mmol of corresponding 2-trifluoromethyl derivative **3a**,**b** or **3'b** and 150 mg (2 mmol) hydroxylamine hydrochloride in 5 mL of anhydrous pyridine was refluxed for 16 h. The reaction mixture was evaporated to dryness under reduced pressure, diluted with 20 mL water and acidified with 1 N HCl to pH 4. The formed precipitate was filtered off, dried at air, and crystallized from MeOH-H_2O (1:1) mixture to afford **10** or **11**.

4-(4-(2-Hydroxyethyl)-3-(trifluoromethyl)isoxazol-5-yl)benzene-1,3-diol (10a). Yield 162 mg (56%); off-white powder; mp 240 – 242 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.15 (s, 1H), 9.93 (s, 1H), 7.24 (d, J = 8.4 Hz, 1H), 6.48 (s, 1H), 6.39 (d, J = 8.4 Hz, 1H), 4.85 – 4.72 (m, 1H), 3.49 – 3.36 (m, 2H), 2.67 (t, J = 7.0 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 169.6, 161.2, 157.0, 153.9 (q, J_{C-F} = 35.2 Hz), 131.6, 120.5 (q, J_{C-F} = 271.6 Hz), 110.6, 107.4, 104.5, 102.9, 59.8, 25.6; ^{19}F NMR (376 MHz, DMSO-d_6): δ -61.6; MS (APCI) *m/z*: 290.0 ([M+H]$^+$, 100); 288.2 ([M-H]$^-$, 100). Anal. Calcd for $C_{12}H_{10}F_3NO_4$: C, 49.84; H, 3.49; N, 4.84. Found: C, 49.70; H, 3.33; N, 4.72.

2-(4-(2-Hydroxyethyl)-3-(trifluoromethyl)isoxazol-5-yl)-5-methoxyphenol (10b). Yield 215 mg (71%); off-white powder; mp 87 – 89 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.40 (s, 1H), 7.38 (d, J = 9.3 Hz, 1H), 6.72 – 6.28 (m, 2H), 4.86 – 4.75 (m, 1H), 3.77 (s, 3H), 3.49 – 3.38 (m, 2H), 2.67 (t, J = 7.0 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 169.2, 162.6, 157.0, 153.9 (q, J_{C-F} = 35.6 Hz), 131.7, 120.4 (q, J_{C-F} = 271.2 Hz), 111.1, 106.1, 105.7, 101.6, 59.8, 55.2, 25.6; ^{19}F NMR (470 MHz, DMSO-d_6): δ -61.6; MS (APCI) *m/z*: 304.2 ([M+H]$^+$, 100); 302.2 ([M-H]$^-$, 100). Anal. Calcd for $C_{13}H_{12}F_3NO_4$: C, 51.49; H, 3.99; N, 4.62. Found: C, 51.69; H, 3.87; N, 4.51.

3-(2-Hydroxy-4-methoxyphenyl)-4-(2-hydroxyethyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-5-ol (11). Yield 228 mg (71%); off-white powder; mp 175 – 177 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.59 (s, 1H), 7.68 (d, J = 8.7 Hz, 1H), 6.72 – 6.64 (m, 2H), 6.62 – 6.56 (m, 1H), 4.32 – 3.99 (m, 3H), 3.77 (s,

3H), 2.75 – 2.58 (m, 1H), 1.99 – 1.73 (m, 1H); ^{13}C NMR (150 MHz, DMSO-d_6): δ 162.4, 153.4, 146.2, 125.0, 122.7 (q, J_{C-F} = 286.4 Hz), 111.0, 108.4, 103.6 (q, J_{C-F} = 33.0 Hz), 70.1, 55.9, 36.5, 28.6; ^{19}F NMR (376 MHz, DMSO-d_6): δ -81.6; MS (APCI) *m/z*: 304.2 ([M-H_2O+H]$^+$, 100); 302.2 ([M-H_2O-H]$^-$, 100). Anal. Calcd for $C_{13}H_{14}F_3NO_5$: C, 48.60; H, 4.39; N, 4.36. Found: C, 48.73; H, 4.25; N, 4.48.

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