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Chemoselective synthesis of 3-trifluoromethylpyrazole-deoxybenzoin hybrids



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 A R T I C L E I N F O
 A B S T R A C T

 Keywords:
 A simple method of the synthesis of α-(3(5)-trifluoromethylpyrazol-5(3)-yl)-2-hydroxydeoxybenzoins by a che-moselective reaction of 2-(1,1,1-trifluoroacetonyl)chromones with hydrazine dihydrochloride was developed. This approach involves the initial attack of hydrazine at the carbonyl atom of the CF₃C(O)CH₂ group followed by the chromone ring opening at C-2 atom and subsequent cyclization to pyrazoles. Such synthetic strategy provides easy access to the novel type of pharmaceutically attractive 3-(trifluomethyl)pyrazole-deoxybenzoin hybrids in high yields.

1. Introduction

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The development of simple methods of the synthesis of trifluoromethylated heterocycles is an active area of research because of their broad spectrum of unique biological and physiological activities. Thus, trifluoromethyl substituted pyrazoles display various biological activities [1] and constitute the core of several pharmacological agents. The most known examples (Fig. 1) include celecoxib [2] (1a) and mavacoxib [3] (1b) as COX-2 inhibitors, SC-560 [4] (1c) as a selective COX-1 inhibitor, and Razaxaban [5], an oral factor Xa inhibitor that was being developed for the treatment of thrombosis. Recent studies have also shown that polyhydroxylated 3,4-diaryl-5-trifluoromethylpyrazoles represent a promising scaffold for targeting glycogen synthase activity in the glycogen synthase diseases associated with an excess of glycogen accumulation [6]. Therefore, the development of new methods of synthesis of various derivatives of trifluoromethylated pyrazoles is of great interest, which was evident by recent publications [7].

On the other hand, isolated from various plants [8] deoxybenzoins 2 (Fig. 1) as wel as their synthetic analogs posses various biological activities. Considerable attention was focused on polyhydroxylated deoxybenzoins because of their antioxidant [9], radical-scavenging [10] properties and also their effectiveness as selective estrogen receptor

modulators [11].

Most of the reported procedures devoted to the synthesis of 3(5)-arylpyrazoles, while the synthesis of the related 3-phenacylpyrazoles is represented by several examples. For example, these compounds were obtained by a two-step procedure from 3-halo-2-styrylchromones [12], and as bypass products in the synthesis of pyrazolo[4,3-c]pyridines by condensation of 1-aryl-5-chloro-4-formyl-3-trifluoromethylpyrazoles with *tert*-butylamine under a microwave irradiation [13]. The reaction of acyl/aryl hydrazones with esters [14] and water addition to phenylethynylpyrazoles [15] led to the similar 3-phenacylpyrazoles. Finally, Dess-Martin oxidation of 1-phenyl-2-(3-pyrazolyl)ethanol resulted in the synthesis of 3-phenacylpyrazoles, which displayed inhibition of the West Nile Virus NS2B-NS3 protease [16]. Moreover, neither of these examples led to trifluoromethyl substituted phenacylpyrazoles.

The trifluoromethyl-containing chromones possess a remarkable place in the synthesis of trifluoromethylated pyrazoles bearing 2hydroxyphenyl/2-salicyloyl moieties. Thus, the reaction of 2-trifluoromethylchromones with hydrazine is widely used as an efficient method for the synthesis of 3-(2-hydroxyphenyl)-5-trifluoro methylpyrazoles [17]. Typically, such reaction is initiated by the attack of hydrazine on C-2 atom of the chromone ring followed by further cascade ring-opening and ring-closure reactions leading to the pyrazoles

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Fig. 1. Bioactive trifluoromethylpyrazoles 1 and deoxybenzoins 2.

[18]. However, it has been shown that in case of 2-hydroxy-2-polyfluoroalkylchroman-4-ones the reaction with hydrazine derivatives can proceed through the initial attack on either C-2 or C-4 atom, depending on the nature of the hydrazine substituent to afford different pyrazole/pyrazoline regioisomers [17a]. Reactions of 3-(polyfluoroacyl) chromones with hydrazine, methyl- and phenylhydrazines proceed by the mechanism of nucleophilic 1,4-addition with subsequent pyrone ring opening and heterocyclization at the polyfluoroacyl group to 4-(2-hydroxyaroyl)-3-polyfluoro-alkylpyrazoles or at the aroyl group to 4-polyfluoroalkyl-2,4-dihydrochromeno[4,3-c]pyrazol-4-ols [19].

However, there is no precedent in the literature on the reactions of chromones bearing carbonylalkyl groups in positions 2 or 3 with bidentate nucleophiles. In this work we describe an efficient protocol for the synthesis of deoxybenzoin-pyrazole hybrids using an unexpected reaction of recently reported 2-(1,1,1-trifluoroacetonyl)isoflavones [20] with hydrazine dihydrochloride.

2. Results and discussion

Surprisingly, application of the common procedure for the synthesis of pyrazoles from chromone 3a and hydrazine hydrate under reflux in alcohols did not led to pyrazoles (Table 1, entries 1 and 2). Partially, we explain such an outcome by the gem-diol nature of the compound 3a [20] that could prevent the attack of hydrazine at the carbon adjacent to CF3 group. However, this fact does not explain the absence of well-known formation of 3(5)-(2-hydroxyphenyl)pyrazoles, synthesis of which do not depend on the chromone C-2 substituent. We assumed that

Table 1

Optimization on reaction	of isoflavone	3a with	hydrazine	or its	salt
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using of various solvents could alter the nucleophilicity of hydrazine or its salts and result in the reaction (Table 1, entries 3-8). We also expected that carrying out reaction under acidic conditions would cause the conversion of a gem-diol to keto/enol/enol ether form and thus would promote the attack of hydrazide at carbonyl group of the trifluoroacetonyl fragment and following cyclization to C-2 or C-4 carbon atom. Indeed, the refluxing of compound 3a with hydrazine dihydrochloride in anhydrous ethanol resulted in the reaction and afforded 3-trifloromethylpyrazole 4a. Interestingly, that use of i-PrOH or PrOH as solvents apart from 4a provided a significant amount of 2-methylformononetin (3'a) as a side product of CH₂-CO bond cleavage. In addition, refluxing 3a with hydrazine sulfate in alcohols furnished pyrazole 4a in small vield.

The structure of pyrazole 4a was confirmed by two-dimensional NMR techniques. For instance, in HMBC spectra a correlation between: H-6 proton of the phenolic ring and the carbonyl group at δ_{C} 198.98 ppm; H-4" pyrazole proton and C-5 atom of the pyrazole ring; H-2'(6') protons of anisole fragment and CH carbon at δ_C 48.58 ppm adjacent to carbonyl group were observed (Fig. 2). These correlations were possible only for compound with general structure related to deoxybenzoin-pyrazole hybrid 4a.

Next, with the purpose to determine an influence of the substituents in isoflavone A and B rings on the scope of this transformation we investigated the reaction of variously substituted 2-(1,1,1-trifluoroacetonyl)isoflavones 3b-3k (see Supporting info). It turned out that substituents did not have significant influence and in all cases the reaction led to the formation of B-ring substituted deoxybenzoinpyrazole hybrids 4b-4g and 5a-5d in decent yields. (Table 2).

The developed reaction conditions proved to be also suitable for the synthesis of polyhydroxypyrazoles 5b and 5c with "phloroglucinol" fragment, while the reported synthesis of related 3-(2,4,6-trihydroxyphenyl)pyrazoles usually requires protection of hydroxyl group in chromones and their following deprotection in pyrazoles [21]. Moreover, the reaction of non-tolerant to nucleophiles Mannich bases 31-30 with hydrazine dihydrochloride under the developed conditions also led



Fig. 2. Principal correlations in HMBC spectrum of compound 4a.

HO Ja	Teagent HO conditions HO OMe 4a OF	HN HN O O Me	O Me O OMe	
Entry	Solvent	Temp. (°C)	Reagent	LC yield of 4a (%)
1	EtOH	78	N ₂ H ₄ ·H ₂ O	_ [b]
2	<i>i</i> -PrOH	80	N ₂ H ₄ ·H ₂ O	_ [b]
3	abs. EtOH	78	N ₂ H ₄ ·2HCl	87, ^[c] (96:4) ^[d]
4	<i>i</i> -PrOH	80	N ₂ H ₄ ·2HCl	72, ^[c] (91:9) ^[d]
5	PrOH	80	N ₂ H ₄ ·2HCl	70, ^[c] (90:10) ^[d]
6	abs. EtOH	78	N ₂ H ₄ ·H ₂ SO ₄	36
7	<i>i</i> -PrOH	80	N ₂ H ₄ ·H ₂ SO ₄	-
8	PrOH	80	N_2H_4 · H_2SO_4	_

^[a]Reaction conditions: **3a** (1 mmol), hydrazine derivative (2 equiv), solvent (5 mL), N₂ atmosphere, heating for 16 h; ^[b] formation of enol ether was detected by LC-MC. ^[c] isolated yield; ^[d] ratio of pyrazole : 2-methylformononetin (3'a).

Table 2

Product scope of the reaction of 2-trifluoroacetonylisoflavones with hydrazine dihydrochloride.



to the formation of related pyrazoles 6a-6d (Table 2).

Besides 2-(3,3,3-trifluoro-1-methyl-2-oxopropyl)-4*H*-chromen-4ones **3p** and **3q** easily reacted with hydrazine dihydrochloride to afford corresponding 4-methylpyrazoles **7a** and **7b** in 87 % and 75 % yields respectively (Scheme 1).

The structure of the synthesized pyrazoles encouraged us to investigate a plausible mechanism of the reaction of 2-(3,3,3-trifluoro-1methyl-2-oxopropyl)isoflavones with hydrazine dihydrochloride. As it was mentioned above, typically the reactions of various chromone derivatives with hydrazine tend to be initiated by the attack of the latter at C-2 atom leading to the formation of intermediates **8** and followed by the ring opening and subsequent intramolecular cyclization [18]. We concluded that for the given reaction such pathway (Path A, Scheme 2) was not the case, otherwise adducts **9** would undergo the ring-closure reaction leading to the formation of target compounds **4-7** as well as of the alternative compounds **10**, a formation of which was not observed. Moreover, the absence of reaction between compound **3a** and hydrazine hydrate serves as additional evidence against pathway A (Table 1, entries 1–3).

Most likely, the reaction proceeds through the initial acid-promoted nucleophilic attack of hydrazine at trifluoroacetonyl group (or *in situ* formed enol ether/hemi-ketal) furnishing compounds **11** (or their corresponding hydrazones) and the subsequent intramolecular attack at



Scheme 1. Synthesis of 4-methyl-3-trifluoromethylpyrazoles 7a, 7b.



Scheme 2. A tentative mechanism of the reaction of trifluoroacetonylchromones with hydrazine dihydrochloride.

chromone C-2 atom leading to the ring-opening of chromone core and following cyclization to pyrazoles **4-7**. We did not detect the formation of alternative 3-(2-hydroxyphenyl)-7-(trifluoromethyl)-1,4-dihydro-5*H*-1,2-diazepin-5-ones **12** that would result from the hydrazine attack at C-4 atom of the chromone ring. Obviously, such direction of the reaction was less favorable due to the formation of seven-membered heterocyclic ring. Moreover, the recently reported reactions of 2-trifluoroacetylchromones with N- or C-nucleophiles involving only trifluoroacetyl group could also serve as an indirect support of the proposed mechanism [22].

To prove the suggested mechanism, we have also investigated the interaction of 2-(1,1,1-trifluoroacetonyl)chromones with hydroxylamine hydrochloride. As it was reported earlier [23], the initial nucleophilic attack of hydroxylamine hydrochloride at C-2 unsubstituted isoflavones depended on solvent and additional bases, while substituents such as Me or CF_3 groups promoted the initial C-2 attacks of chromone core in pyridine.

Our attempts to carry out the reaction of compounds **3a**, **3b** with hydroxylamine hydrochloride in pyridine were completely unsuccessful. On the other hand, the reaction of the compound **3a**, **3b** with hydroxylamine hydrochloride in anhydrous ethanol resulted in oximes **13a** and **13b** without affecting of the chromone ring (Scheme 3). These results also served as an additional confirmation of the primary attack of bidentate nucleophiles at exocyclic carbonyl group of trifluoroacetonyl fragment of 2-(1,1,1-trifluoroacetonyl)isoflavones.

3. Conclusions

In summary, the reaction of the 2-(3,3,3-trifluoro-2-oxopropyl) chromones with hydrazine dihydrochloride involved the initial attack of



Scheme 3. Reaction of 2-(3,3,3-trifluoro-2-oxopropyl)chromones **3a** and **3b** with hydroxylamine dihydrochloride.

hydrazine at CF_3CO group followed by the attack at C-2 atom of the chromone core led to a new pattern of recyclization reaction of chromone ring and provided rapid access to the 3-trifluoromethylpyrazole-deoxybenzoin hybrids. The studies on the biological activity of the synthesized compounds are underway and will be reported in due course.

4. Experimental

4.1. General

¹H, ¹³C, and 2D NMR spectra were recorded on Varian 500 (500/ 125 MHz) or Varian 400 (400/100 MHz) spectrometers in CDCl₃ [residual CHCl₃ ($\delta_{\rm H}$ =7.26 ppm) or CDCl₃ ($\delta_{\rm C}$ =77.16 ppm) as internal standard] or DMSO-*d*₆ [residual SO(CD₃)(CD₂H) ($\delta_{\rm H}$ =2.50 ppm) or SO (CD₃)₂ ($\delta_{\rm C}$ =39.52 ppm) as internal standard]. ¹⁹F NMR spectra were recorded on Varian 400 (376 MHz) spectrometers in CDCl₃ or DMSO-*d*₆ [CFCl₃ as external standard]. Melting points were determined in open capillary tubes using Buchi 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. Column chromatography was performed using Macherey-Nagel Silica 60, 0.04–0.063 mm silica gel.

4.2. General procedure for the synthesis of 3-trifluoromethyl pyrazoles 4-7

A mixture of 1 mmol of corresponding chromone **3** and 210 mg (2 mmol) hydrazine dihydrochloride in 5 mL anhydrous ethanol was refluxed for 16 h. The reaction mixture was concentrated in vacuum, diluted with 20 mL of water, and neutralized with saturated aqueous solution of NaHCO₃. A formed precipitate was collected by filtration and purified by column chromatography using benzene-acetone mixture (2:1) as an eluent.

4.2.1. 1-(2,4-Dihydroxyphenyl)-2-(4-methoxyphenyl)-2-[3(5)-(trifluoromethyl)-1H-pyrazol-5(3)-yl]ethanone (4a)

White solid (341 mg, 87 % yield); mp 101–103 °C; ¹H NMR (400 MHz, DMSO- d_6): δ 3.72 (3H, s, 4'-OCH₃), 6.26 (1H, d, J =2.2 Hz, H-3), 6.29 (1H, s, H-4''), 6.35 (2H, dd, J =9.0 Hz, J =2.2 Hz, H-5), 6.37 (1H, s, COCH), 6.93 (2H, d, J =8.6 Hz, H-3', 5'), 7.36 (2H, d, J =8.6 Hz, H-2', 6'), 7.88 (1H, d, J =9.0 Hz, H-6), 12.18 (1H, s, 2-OH), 13.52 ppm (1H, s, NH); ¹³C NMR (100 MHz, DMSO- d_6): δ 48.58 (C(O)CH), 55.09 (OCH₃), 102.69 (CH-3), 103.57 (CH-4''), 108.70 (CH-5), 111.53 (C-1), 114.46 (CH-3', 5'), 121.77 (CF₃, q, $J_{C,F}$ =267.9 Hz), 129.02 (C-1'), 129.68 (CH-2', 6'), 133.41 (CH-6), 140.35 (C-3'', q, $J_{C,F}$ =37.9 Hz), 143.80 (C-5''), 158.69 (C-4'), 164.74 (C-2), 165.46 (C-4), 198.98 ppm (C = O); ¹⁹F NMR (376 MHz, DMSO- d_6): δ -60.32 ppm; MS (APCI): (m/z) 393.2 ([M+H]⁺, 100); 391.2 ([M-H]⁻, 100). Anal. calcd for C₁₉H₁₅F₃N₂O₄: C 58.17; H, 3.85; N, 7.14; found: C, 58.03; H, 3.99; N, 7.03.

4.2.2. 1-(2,4-Dihydroxyphenyl)-2-phenyl-2-[3(5)-(trifluoromethyl)-1H-pyrazol-5(3)-yl]ethanone (4b)

White solid (210 mg, 58 % yield); mp 99–101 °C; ¹H NMR (400 MHz, DMSO- d_6): δ 6.26–6.41 (3H, m, H-3, 5, 4″), 6.46 (1H, s, COCH), 7.08–7.62 (5H, m, Ph), 7.89 (1H, d, J =9.0 Hz, H-6), 10.79 (1H, s, 4-OH), 12.15 (1H, s, 2-OH), 13.58 ppm (1H, s, NH); ¹³C NMR (100 MHz, DMSO- d_6): δ 49.63, 102.91, 103.80, 108.84, 111.91, 121.90 (q, $J_{C,F}$ = 267.9 Hz), 127.82, 128.66, 129.16, 133.56, 137.34, 140.85 (q, J_{C} . F = 35.5 Hz), 143.31, 164.91, 165.47, 198.86 ppm; ¹⁹F NMR (376 MHz, DMSO- d_6): δ -60.87 ppm; MS (APCI): (m/z) 363.0 ([M+H]⁺, 100); 361.0 ([M-H]⁻, 100). Anal. calcd for C₁₈H₁₃F₃N₂O₃: C, 59.67; H, 3.62; N, 7.73; found: C, 59.41; H, 3.50; N, 7.98.

4.2.3. 1-(2,4-Dihydroxyphenyl)-2-(4-hydroxyphenyl)-2-[3(5)-

(*trifluoromethyl*)-1*H*-pyrazol-5(3)-yl]ethanone (4c) White solid (246 mg, 65 % yield); mp 138–140 °C; ¹H NMR (400 MHz, DMSO-*d*₆): δ 6.24–6.28 (2H, m, H-3, 4″), 6.30 (1H, s, COCH), 6.35 (1H, dd, J = 8.9, 2.4 Hz, H-5), 6.74 (2H, d, J =8.6 Hz, H-3', 5'), 7.23 (2H, d, J = 8.6 Hz, H-2', 6'), 7.87 (1H, d, J =8.9 Hz, H-6), 9.52 (1H, s, 4'-OH), 10.76 (1H, s, 4-OH), 12.20 (1H, s, 2-OH), 13.48 (1H, s, NH); ¹³C NMR (100 MHz, DMSO-*d*₆): δ 48.70, 102.84, 103.68, 108.72, 111.71, 115.98, 121.94 (q, $J_{C,F}$ =267.9 Hz), 127.38, 129.77, 133.55, 140.65 (q, $J_{C,F}$ = 36.8 Hz), 143.94, 157.09, 164.96, 165.31, 199.44 ppm; ¹⁹F NMR (376 MHz, DMSO-*d*₆): δ -55.55 ppm; MS (APCI): (*m*/*z*) 377.0 ([M-H]⁻, 100). Anal. calcd for C₁₈H₁₃F₃N₂O₄: C, 57.15; H, 3.46; N, 7.41; found: C, 56.90; H, 3.18; N, 7.66.

4.2.4. 1-(2,4-Dihydroxyphenyl)-2-(2-methoxyphenyl)-2-[3(5)-(trifluoromethyl)-1H-pyrazol-5(3)-yl]ethanone (4d)

White solid (302 mg, 77 % yield); mp 99–97 °C; ¹H NMR (400 MHz, DMSO- d_6): δ 3.81 (3H, s, 2'-OCH₃), 6.24–6.30 (1H, m, H-4''), 6.31–6.40 (2H, m, H-3, 5), 6.51 (1H, s, COCH), 6.89–6.99 (1H, m, H-5'), 7.02–7.11 (2H, m, H-3', 6'), 7.25–7.35 (1H, m, H-4'), 7.70 (1H, d, J =8.9 Hz, H-6), 10.75 (1H, s, 4-OH), 12.08 (1H, s, 2-OH), 13.57 ppm (1H, s, NH); ¹³C NMR (100 MHz, DMSO- d_6): δ 43.38, 55.85, 102.73, 103.85, 108.67, 111.56, 111.61, 120.86, 121.76 (q, $J_{C,F}$ =267.8 Hz), 125.46, 128.60, 129.24, 132.54, 140.62 (q, $J_{C,F}$ = 37.0 Hz), 142.00, 155.72, 164.54, 165.11, 199.06 ppm; ¹⁹F NMR (376 MHz, DMSO- d_6): δ -60.34 ppm; MS (APCI): (m/z) 393.2 ([M+H]⁺, 100); 391.0 ([M-H]⁻, 100). Anal. calcd for C₁₉H₁₅F₃N₂O₄: C, 58.17; 3.85; N, 7.14; found: C, 57.92; 3.77; N, 7.39.

4.2.5. 1-(2,4-Dihydroxyphenyl)-2-(3,4-dimethoxyphenyl)-2-[3(5)-(trifluoromethyl)-1H-pyrazol-5(3)-yl]ethanone (4e)

White solid (363 mg, 86 % yield); mp 108–111 °C; ¹H NMR (400 MHz, DMSO- d_6): δ 3.72, 3.74 (3H, 3H, 2 s, 3', 4'-OCH₃), 6.28 (1H, s, H-4''), 6.30–6.42 (3H, m, H-3, 5, COCH), 6.93 (2H, s, H-2', 6'), 7.07 (1H, s, H-5'), 7.89 (1H, d, J =8.9 Hz, H-6), 10.67 (1H, s, 4-OH), 12.14 (1H, s, 2-OH), 13.45 ppm (1H, s, NH); ¹³C NMR (100 MHz, DMSO- d_6): δ 49.42, 55.83, 55.97, 103.05, 104.03, 108.96, 112.05, 112.52, 112.63, 121.02, 122.19 (q, $J_{C,F}$ =268.1 Hz), 129.60, 133.85, 140.82 (q, $J_{C,F}$ = 39.9 Hz), 143.95, 148.73, 149.37, 165.12, 165.55, 199.41 ppm; ¹⁹F NMR (376 MHz, DMSO- d_6): δ -60.31 ppm; MS (APCI): (m/z) 423.0 ([M+H]⁺, 100); 421.0 ([M-H]⁻, 100). Anal. calcd for C₂₀H₁₇F₃N₂O₅: C, 56.88; 4.06; N, 6.63; found: C, 57.11; 4.21; N, 6.88.

4.2.6. 2-(3,4-Dichlorophenyl)-1-(2,4-dihydroxyphenyl)-2-[3(5)-(trifluoromethyl)-1H-pyrazol-5(3)-yl]ethanone (4f)

White solid (328 mg, 76 % yield); mp 109–111 °C; ¹H NMR (400 MHz, DMSO- d_6): δ 6.27 (1H, s, H-4″), 6.32–6.39 (1H, m, H-5), 6.45 (1H, s COCH), 6.51 (1H, s, H-3), 7.30–7.42 (1H, m, H-6′), 7.63 (1H, d, J = 8.3 Hz, H-6), 7.67–7.77 (1H, m, H-2′), 7.83 (1H, d, J = 8.9 Hz, H-5′), 11.91 (1H, s, 2-OH), 13.66 ppm (1H, s, NH); ¹³C NMR (100 MHz, DMSO- d_6): δ 48.64, 102.70, 103.62, 108.96, 111.68, 121.57 (q, $J_{C,F}$ = 267.9 Hz), 128.91, 130.50, 130.64, 130.98, 131.33, 133.24, 137.94, 140.41 (q, $J_{C,F}$ = 39.9 Hz), 142.53, 164.28, 165.86, 196.87 ppm; ¹⁹F NMR (376 MHz, DMSO- d_6): δ -60.8 ppm; MS (APCI): (*m*/*z*) 433.0 ([M (³⁵Cl³⁷Cl)+H]⁺, 62); 431.0 ([M(³⁵Cl₂)+H]⁺, 100); 431.0 ([M(³⁵Cl³⁷Cl)-H]⁻, 62); 429.0 ([M(³⁵Cl₂)-H]-, 100). Anal. calcd for C1₈H₁₁Cl₂F₃N₂O₃: C, 50.14; 2.57; N, 6.50; found: C, 50.27; 2.34; N, 6.71.

4.2.7. 2-(4-Bromophenyl)-1-(2,4-dihydroxyphenyl)-2-[3(5)-(trifluoromethyl)-1H-pyrazol-5(3)-yl]ethanone (4g)

White solid (313 mg, 71 % yield); mp 123–125 °C; ¹H NMR (400 MHz, DMSO- d_6): δ 6.25 (1H, d, J =2.2 Hz, H-3), 6.29–6.37 (2H, m, H-5, 4''), 6.44 (1H, s, 1H, s, COCH), 7.34 (2H, d, J =8.4 Hz, H-3', 5'), 7.53 (2H, d, J =8.4 Hz, H-2', 6'), 7.82 (1H, d, J =9.0 Hz, H-6), 10.76 (1H, s, 4-OH), 11.99 (1H, s, 2-OH), 13.55 ppm (1H, s, NH); ¹³C NMR (100 MHz, DMSO- d_6): δ 49.00, 102.73, 103.67, 108.76, 111.87, 121.11,

121.73 (q, $J_{C,F}$ =269.4 Hz), 130.85, 131.95, 133.42, 136.54, 140.67 (d, $J_{C,F}$ = 35.7 Hz), 142.79, 164.47, 165.37, 198.02 ppm; ¹⁹F NMR (376 MHz, DMSO- d_6): δ -60.36 ppm; MS (APCI): (m/z) 443.0 ([$M(^{81}Br)$ +H]⁺, 100); 441.0 ([$M(^{79}Br)$ +H]⁺, 97); 441.0 ([$M(^{81}Br)$ -H]⁻, 100); 439.0 ([$M(^{79}Br)$ -H]⁻, 95). Anal. calcd for C₁₈H₁₂BrF₃N₂O₃: C, 49.00; 2.74; N, 6.35; found: C, 48.74; 2.58; N, 6.60.

4.2.8. 1-(2-Hydroxy-4-methoxyphenyl)-2-(4-methoxyphenyl)-2-[3(5)-(trifluoromethyl)-1H-pyrazol-5(3)-yl]ethanone (5a)

White solid (301 mg, 74 % yield); mp 53–55 °C; ¹H NMR (400 MHz, DMSO- d_6): δ 3.23, 3.29 (3H, 3H, 2 s, 4, 4'-OCH₃), 5.47 (1H, s, H-4''), 5.82–5.95 (3H, m, H-3, 5, COCH,), 6.34 (2H, d, *J* =8.3 Hz, H-3', 5'), 6.72 (2H, d, *J* =8.3 Hz, H-2', 6'), 7.18 (1H, d, *J* =8.8 Hz, H-6), 11.94 ppm (1H, s, 2-OH); ¹³C NMR (100 MHz, DMSO- d_6): δ 48.97, 55.44, 55.85, 101.28, 103.87, 108.67, 112.03, 114.95, 121.26 (q, *J*_{C.F} =268.2 Hz), 128.42, 129.09, 131.85, 142.59 (q, *J*_{C.F} =38.7 Hz), 142.66, 159.34, 166.52, 166.76, 199.57 ppm; ¹⁹F NMR (376 MHz, DMSO- d_6) δ -62.51 ppm; MS (APCI): (*m*/*z*) 407.0 ([M+H]⁺, 100); 405.0 ([M-H]⁻, 100). Anal. calcd for C₂₀H₁₇F₃N₂O₄: C, 59.11; 4.22; N, 6.89; found: C, 59.35; 4.40; N, 6.97.

4.2.9. 1-(2,6-Dihydroxy-4-methoxyphenyl)-2-(4-methoxyphenyl)-2-[3 (5)-(trifluoromethyl)-1H-pyrazol-5(3)-yl]ethanone (5b)

White solid (266 mg, 63 % yield); mp 187–189 °C; ¹H NMR (400 MHz, DMSO- d_6): δ 3.71, 3.72 (3H, 3H, 2 s, 4, 4'-OCH₃), 5.94 (2H, s, H-3, 5), 6.27–6.36 (1H, m, H-4''), 6.61 (1H, s, COCH), 6.90 (2H, d, J = 8.7 Hz, H-3', 5'), 7.22 (2H, d, J = 8.7 Hz, H-2', 6'), 12.19 (2H, s, 2, 6-OH), 13.54 ppm (1H, s, NH); ¹³C NMR (100 MHz, DMSO- d_6): δ 51.87, 55.07, 55.47, 93.45, 103.33 (q, $J_{C,F} = 2.2$ Hz), 104.18, 114.03, 121.85 (q, $J_{C,F} = 268.0$ Hz), 129.35, 129.93, 140.49 (q, $J_{C,F} = 36.7$ Hz), 144.09, 158.52, 163.82, 166.05, 200.24 ppm; ¹⁹F NMR (376 MHz, DMSO- d_6): δ -60.29 ppm; MS (APCI): (m/z) 423.1 ($[M+H]^+$, 100); 421.0 ($[M-H]^-$, 100). Anal. calcd for C₂₀H₁₇F₃N₂O₅: C, 56.88; 4.06; N, 6.63; found: C, 56.69; 4.21; N, 6.79.

4.2.10. 2-(4-Chlorophenyl)-1-(2,6-dihydroxy-4-methoxyphenyl)-2-[3(5)-(trifluoromethyl)-1H-pyrazol-5(3)-yl]ethanone (5c)

White solid (346 mg, 81 % yield); mp 229–231 °C; ¹H NMR (400 MHz, DMSO- d_6): δ 3.73 (3H, s, 4-OCH₃), 5.95 (2H, s, H-3, 5), 6.36 (1H, s, H-4''), 6.65 (1H, s, COCH), 7.30 (2H, d, J =8.2 Hz, H-3', 5'), 7.41 (2H, d, J =8.2 Hz, H-2', 6'), 12.15 (2H, s, 2, 6-OH), 13.58 ppm (1H, s, NH);¹³C NMR (100 MHz, DMSO- d_6): δ 52.22, 55.49, 93.53, 103.44, 104.29, 121.82 (q, $J_{C,F}$ =268.2 Hz), 128.61, 130.71, 132.22, 136.57, 140.73 (q, $J_{C,F}$ =37.3 Hz), 143.25, 163.88, 166.31, 199.48 ppm; ¹⁹F NMR (376 MHz, DMSO- d_6): δ -60.75 ppm; MS (APCI): (m/z) 429.1 ([M (³⁷Cl)+H]⁺, 30); 427.0 ([M(³⁵Cl)+H]⁺, 100); 426.9 ([M(³⁷Cl)-H]⁻, 30) 425.0 ([M(³⁵Cl)+H]⁻, 100). Anal. calcd for C₁₉H₁₄ClF₃N₂O₄: C, 53.47; 3.31; N, 6.56; found: C, 53.22; 3.44; N, 6.38.

4.2.11. 1-(2-hydroxy-4,6-dimethoxyphenyl)-2-(4-methoxyphenyl)-2-[3 (5)-(trifluoromethyl)-1H-pyrazol-5(3)-yl]ethanone (5d)

White solid (231 mg, 53 % yield); mp 70–72 °C; ¹H NMR (400 MHz, CDCl₃): δ 3.76 (3H, s) and 3.81 (6H, s, 4, 6, 4'-OCH₃), 5.89 (1H, s) and 6.08 (1H, s, H-3, 5), 6.36 (1H, s, H-4''), 6.42 (1H, s, COCH), 6.84 (2H, d, J = 7.2 Hz, H-3', 5'), 7.18 (2H, d, J = 7.2 Hz, H-2', 6'), 11.20 (1H, s, 2-OH), 13.49 ppm (1H, s, NH); ¹³C NMR (100 MHz, CDCl₃): δ 52.73, 55.31, 55.73, 55.77, 91.57, 94.12, 103.59, 105.04, 114.47, 121.49 (q, J C,F = 268.5 Hz), 129.21, 129.45, 142.69 (q, J C,F = 3 7.5 Hz), 143.79, 159.14, 162.08, 167.13, 168.57, 200.45 ppm; ¹⁹F NMR (376 MHz, CDCl₃): δ -62.56 ppm; MS (APCI): (m/z) 437.2 ([M+H]⁺, 100); 435.0 ([M-H]⁻, 100). Anal. calcd for C₂₁H₁₉F₃N₂O₅: C, 57.80; 4.39; N, 6.42; found: C, 58.07; 4.22; N, 6.20.

4.2.12. 1-{3-[(Dimethylamino)methyl]-2,4-dihydroxyphenyl}-2-(4methoxyphenyl)-2-[3(5)-(trifluoromethyl)-1H-pyrazol-5(3)-yl]ethanone (6a)

White solid (409 mg, 91 % yield); mp 216–218 °C; ¹H NMR (400 MHz, DMSO- d_6): δ 2.47 (6H, s, N(CH₃)₂), 3.72 (3H, s, 4'-OCH₃), 3.88 (2H, s, 3-CH₂), 6.14 (1H, d, *J* =9.1 Hz, H-5), 6.30 (1H, s, H-4''), 6.32 (1H, s, COCH), 6.92 (2H, d, *J* =8.8 Hz, H-3', 5'), 7.38 (2H, d, *J* =8.8 Hz, H-2', 6'), 7.77 ppm (1H, d, *J* =9.1 Hz, H-6); ¹³C NMR (100 MHz, DMSO- d_6): δ 42.77, 47.50, 53.08, 55.02, 103.35, 105.40, 107.83, 110.74, 114.23, 121.68 (q, *J*_{C.F} =267.8 Hz), 129.42, 129.49, 132.18, 140.15 (q, *J*_{C.F} = 36.7 Hz), 143.96, 158.43, 163.76, 171.35, 196.91 ppm; ¹⁹F NMR (376 MHz, DMSO- d_6): δ -60.73 ppm; MS (APCI): (*m*/*z*) 450.2 ([M+H]⁺, 100); 448.2 ([M-H]⁻, 100). Anal. calcd for C₂₂H₂₂F₃N₃O₄: C, 58.79; 4.93; N, 9.35; found: C, 59.02; 4.75; N, 9.11.

4.2.13. 1-{3-[(Dimethylamino)methyl]-2,4-dihydroxyphenyl}-2-phenyl-2-[3(5)-(trifluoromethyl)-1H-pyrazol-5(3)-yl]ethanone (6b)

White solid (344 mg, 82 % yield); mp 228–230 °C; ¹H NMR (400 MHz, DMSO- d_6): δ 2.45 (6H, s, N(CH₃)₂), 3.86 (2H, s, 3-CH₂), 6.09 (1H, d, J =9.1 Hz, H-5), 6.28–6.43 (2H, m, H-4″, COCH), 7.23–7.52 (5H, m, Ph), 7.73 ppm (1H, d, J =9.1 Hz, H-6); ¹³C NMR (100 MHz, DMSO- d_6): δ 42.74, 48.29, 53.35, 103.45, 103.47, 105.36, 107.59, 111.23, 121.70 (q, $J_{C,F}$ =267.8 Hz), 128.32, 128.83, 132.08, 137.77, 140.23 (q, $J_{C,F}$ = 36.7 Hz), 143.62, 163.91, 172.27, 196.08 ppm; ¹⁹F NMR (376 MHz, DMSO- d_6): δ -60.75 ppm; MS (APCI): (m/z) 420.1 ([M+H]⁺, 100); 418.0 ([M-H]⁻, 100). Anal. calcd for C₂₁H₂₀F₃N₃O₃: C, 60.14; 4.81; N, 10.02; found: C, 60.38; 5.04; N, 10.31.

4.2.14. 1-{3-[(Dimethylamino)methyl]-2,4-dihydroxyphenyl}-2-(2methoxyphenyl)-2-[3(5)-(trifluoromethyl)-1H-pyrazol-5(3)-yl]ethanone (6c)

White solid (382 mg, 85 % yield); mp 224–226 °C; ¹H NMR (400 MHz, DMSO- d_6): δ 2.43 (6H, s, N(CH₃)₂), 3.81 (3H, s, 2'-OCH₃), 3.84 (2H, s, 3-CH₂), 6.11 (1H, d, *J* =9.1 Hz, H-5), 6.36 (1H, s, H-4''), 6.46 (1H, s, COCH), 6.88–6.97 (1H, m, H-5'), 7.06 (1H, d, *J* =8.3 Hz, H-6'), 7.11–7.19 (1H, m, H-3'), 7.23–7.34 (1H, m, H-4'), 7.56 ppm (1H, d, *J* =9.1 Hz, H-6); ¹³C NMR (100 MHz, DMSO- d_6): δ 42.03, 42.88, 53.44, 55.83, 103.74, 105.62, 107.66, 110.99, 111.42, 120.72, 121.67 (q, *J*_{C.F} =267.8 Hz), 125.71, 128.52, 128.95, 131.24, 140.43 (q, *J*_{C.F} = 36.8 Hz), 142.62, 155.51, 163.40, 171.61, 196.90 ppm; ¹⁹F NMR (376 MHz, DMSO- d_6): δ -60.72 ppm; MS (APCI): (*m*/*z*) 450.1 ([M+H]⁺, 100); 448.0 ([M-H]⁻, 100). Anal. calcd for C₂₂H₂₂F₃N₃O₄: C, 58.79; 4.93; N, 9.35; found: C, 58.56; 5.09; N, 9.43.

4.2.15. 2-(3,4-Dimethoxyphenyl)-1-{3-[(dimethylamino)methyl]-2,4dihydroxyphenyl}-2-[3(5)-(trifluoromethyl)-1H-pyrazol-5(3)-yl]ethanone (6d)

White solid (345 mg, 72 % yield); mp 182–184 °C; ¹H NMR (400 MHz, DMSO- d_6): δ 2.44 (6H, s, N(CH₃)₂), 3.71, 3.74 (3H, 3H, 2 s, 3', 4'-OCH₃), 3.85 (2H, s, 3-CH₂), 6.11 (1H, d, J =9.1 Hz, H-5), 6.26 (1H, s, H-4''), 6.34 (1H, s, COCH), 6.84–7.03 (2H, m, H-2', 6'), 7.10 (1H, s, H-5'), 7.77 ppm (1H, d, J =9.1 Hz, H-6); ¹³C NMR (100 MHz, DMSO- d_6): δ 42.85, 47.97, 53.43, 55.43, 55.57, 103.43, 105.58, 107.81, 110.88, 112.01, 112.11, 120.50, 121.74 (q, $J_{C,F}$ =267.8 Hz), 129.81, 132.10, 140.14 (q, $J_{C,F}$ = 36.5 Hz), 143.93, 148.13, 148.78, 163.69, 171.64, 196.75 ppm; ¹⁹F NMR (376 MHz, DMSO- d_6): δ -60.71 ppm; MS (APCI): (*m*/*z*) 480.1 ([M+H]⁺, 100); 478.0 ([M-H]⁻, 100). Anal. calcd for C₂₃H₂₄F₃N₃O₅: C, 57.62; 5.05; N, 8.76; found: C, 57.85; 5.17; N, 8.92.

4.2.16. 1-(2,4-Dihydroxyphenyl)-2-(4-methoxyphenyl)-2-[4-methyl-3(5)-(trifluoromethyl)-1H-pyrazol-5(3)-yl]ethanone (7a)

White solid (354 mg, 87 % yield); mp 188–190 °C; ¹H NMR (400 MHz, DMSO- d_6): δ 2.04 (3H, s, 4''-CH₃), 3.71 (3H, s, 4'-OCH₃), 6.33 (1H, s, COCH), 6.34–6.43 (2H, m, H-3, 5), 6.92 (2H, d, *J* =8.3 Hz, H-3', 5'), 7.34 (2H, d, *J* =8.3 Hz, H-2', 6'), 7.90 (1H, d, *J* =8.9 Hz, H-6), 10.76 (1H, s, 4-OH), 12.24 (1H, s, 2-OH), 13.24 ppm (1H, s, NH); ¹³C NMR

(100 MHz, DMSO- d_6): δ 7.28, 47.85, 55.07, 102.65, 108.60, 111.32, 111.71, 114.27, 122.40 (q, $J_{C,F}$ =272.0 Hz), 128.88, 129.75, 133.45, 138.75 (br. s), 139.70, 158.45, 164.59, 165.20, 198.99 ppm; ¹⁹F NMR (376 MHz, DMSO- d_6): δ -60.30 ppm; MS (APCI): (m/z) 407.0 ([M+H]⁺, 100); 405.2 ([M-H]⁻, 100). Anal. calcd for C₂₀H₁₇F₃N₂O₄: C, 59.12; 4.22; N, 6.89; found: C, 58.91; 4.03; N, 6.68.

4.2.17. 1-(2-Hydroxy-4-methoxyphenyl)-2-(4-methoxyphenyl)-2-[4-methyl-3(5)-(trifluoromethyl)-1H-pyrazol-5(3)-yl]ethanone (7b)

White solid (315 mg, 75 % yield); mp 56–58 °C; ¹H NMR (400 MHz, CDCl₃): δ 2.12 (3H, s, 4"-CH₃), 3.74 (3H, s, 4'-OCH₃), 3.82 (3H, s, 4-OCH₃), 5.95 (1H, s, COCH), 6.38–6.52 (2H, m, H-3, 5), 6.85 (2H, d, J = 8.7 Hz, H-3', 5'), 7.23 (2H, d, J = 8.7 Hz, H-2', 6'), 7.79 (1H, d, J = 9.8 Hz, H-6), 11.34 (1H, s, 2-OH), 12.46 ppm (1H, s, NH); ¹³C NMR (100 MHz, CDCl₃): δ 8.49, 47.84, 56.12, 56.57, 102.03, 109.48, 112.76, 112.84, 115.63, 122.64 (q, $J_{C,F} = 268.7$ Hz), 128.61, 129.74, 132.46, 139.97, 141.69 (q, $J_{C,F} = 35.3$ Hz), 159.96, 167.35, 167.58, 200.70 ppm; ¹⁹F NMR (376 MHz, CDCl₃): δ -62.09 ppm; MS (APCI): (*m/z*) 421.2 ([M+H]⁺, 100); 419.0 ([M-H]⁻, 100). Anal. calcd for C₂₁H₁₉F₃N₂O₄: C, 60.00; 4.56; N, 6.66; found: C, 59.82; 4.41; N, 6.89.

4.2.18. 7-Hydroxy-3-(4-methoxyphenyl)-2-[(2E)-3,3,3-trifluoro-2-(hydroxyimino)propyl]-4H-chromen-4-one (13a)

A solution of 396 mg (1 mmol) of chromone **3a** and 150 mg (2 mmol) hydroxylamine hydrochloride in 5 mL of anhydrous ethanol was refluxed for 16 h. The reaction mixture was evaporated, diluted with 20 mL water, and neutralized with saturated aqueous solution of NaHCO₃. A formed precipitate was filtered off, dried, and purified by column chromatography using benzene-acetone mixture (2:1) as an eluent. White solid (318 mg, 81 % yield); mp 244–246 °C; ¹H NMR (400 MHz, DMSO-d₆): δ 3.79 (3H, s, 4'-OCH₃), 3.82 (2H, s, 2-CH₂), 6.70 (1H, s, H-8), 6.91 (1H, d, J = 8.8 Hz, H-6), 6.99 (2H, d, J = 7.7 Hz, H-3', 5'), 7.21 (2H, d, J = 7.7 Hz, H-2', 6'), 7.88 (1H, d, J = 8.8 Hz, H-5), 10.74 (1H, s, 7-OH), 12.75 ppm (1H, s, =NOH); ¹³C NMR (125 MHz, DMSO d_6): δ 27.48, 55.08, 101.65, 113.65, 115.18, 115.59, 121.00 (q, $J_{C,F}$ =273.6 Hz), 122.59, 124.55, 127.30, 131.63, 142.32 (q, $J_{C,F} = 31.9$ Hz), 156.88, 158.53, 158.84, 162.77, 175.09 ppm; ¹⁹F NMR (376 MHz, DMSO-*d*₆): δ -66.99 ppm; MS (APCI): (*m*/*z*) 394.0 ([M+H]⁺, 100); 392.0 ([M-H]⁻, 100). Anal. calcd for C₁₉H₁₄F₃NO₅: C, 58.02; 3.59; N, 3.56; found: C, 57.81; 3.78; N, 3.30.

4.2.19. 7-Hydroxy-3-phenyl-2-[3,3,3-trifluoro-2-(hydroxyimino)propyl]-4H-chromen-4-one (13b)

Was synthesized using the similar procedure as described for **13a** from 366 mg (1 mmol) of chromone **3b** and 150 mg (2 mmol) of hydroxylamine to provide 203 mg (56 %) of **13b** as a white solid (mp 230–232 °C; ¹H NMR (400 MHz, DMSO-*d*₆): δ 3.80 (2H, s, 2-CH₂), 6.71 (1H, d, *J* =2.3 Hz, H-8), 6.92 (1H, dd, *J* =8.7 Hz, *J* =2.3 Hz, H-6), 7.24–7.33 (2H, m, H-2', 6'), 7.35–7.49 (3H, m, H-3', 4', 5'), 7.89 (1H, d, *J* =8.7 Hz, H-5), 10.82 (1H, s, 7-OH), 12.80 ppm (1H, s, =NOH); ¹³C NMR (100 MHz, DMSO-*d*₆): δ 27.53, 101.72, 115.31, 115.61, 121.02 (q, *J*_{C.F} =273.2 Hz), 123.01, 127.35, 127.82, 128.21, 130.49, 132.68, 142.25 (q, *J*_{C.F} = 32.3 Hz), 156.96, 158.65, 162.89, 174.95 ppm; ¹⁹F NMR (376 MHz, DMSO-*d*₆): δ -67.10 ppm; MS (APCI): (*m*/*z*) 364.0 ([M+H]⁺, 100); 362.0 ([M-H]⁻, 100). Anal. calcd for C₁₈H₁₂F₃NO₄: C, 59.51; 3.33; N, 3.86; found: C, 59.37; 3.46; N, 3.71.

Declaration of Competing Interest

No conflict of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jfluchem.2020.10 9698.

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I.M. Biletska et al.

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