3-(Polyhaloacyl)chromones and their Hetero Analogues: Synthesis and Reactions with Amines

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Abstract: 2-Hydroxy-2-(polyhaloalkyl)chroman-4-ones react with diethoxymethyl acetate at 140–150 °C for 15 minutes to give 3-(polyhaloacyl)chromones in good yields. The reactions of these compounds with amines proceeds at C-2 with pyrone ring-opening and formation of 2-(alkyl/arylaminomethylene)-2-hydroxy-2-(polyfluoroalkyl)chroman-4-ones.

Key words: chroman-4-ones, diethoxymethyl acetate, formylation, 3-(polyhaloacyl)chromones, amines

The synthetic utility of 2-unsubstituted 3-formyl- and 3-acylchromones derives primarily from the reactivity of their three electron-deficient centres at C-2, C-4 and the 3-formyl or 3-acyl groups. The majority of the reactions with these compounds are nucleophilic additions with concomitant opening of the pyrone ring leading to various types of heterocyclic products. In addition, some of them can react as heterodienes and as dienophiles.[1]

Chromones unsubstituted at C-2 and with 3-formyl or 3-acetyl groups were first prepared in low yields from 3-(2-hydroxyphenyl)-3-oxopropanal and 1-(2-hydroxyphenyl)butane-1,3-dione with ethyl orthoformate and acetic anhydride.[2] The synthesis of 3-acetylchromone has also been achieved by acetylation of 3-(2-hydroxyphenyl)-3-oxopropanal with acetic anhydride/sodium acetate[2,3] and formylation of 1-(2-hydroxyphenyl)butane-1,3-dione with acetic formic anhydride/sodium formate[4a] and dimethylformamide dimethyl acetal.[4b] In 1973, a convenient synthesis of 3-formylchromone from 2-hydroxyacetophenone and the Vilsmeier reagent was reported.[5]

3-Polyfluoroacyl substituted chromones, despite their potential interest as building blocks in organic synthesis for the construction of more complex polyfluoroalkyl-containing heterocycles have not received much attention, probably owing to the lack of general methods for the preparation of these compounds. To the best of our knowledge, there has been only one report on the preparation of 3-(trifluoroacetyl)- and 3-(trichloroacetyl)chromones by the reaction of 3-(dimethylamino)-1-(2-hydroxyphenyl)prop-2-en-1-one with trifluoro- and trichloroacetic anhydrides.[6] The procedure for the synthesis of 3-(trihaloacetyl)chromone and its spectroscopic data were not presented, a surprising fact in view of their potential synthetic utility and the present great interest in 3-formylchromone chemistry.[1,7]

The synthesis of specifically trifluoromethylated molecules is an ongoing area of research due to the unique physical and biological properties imparted by the CF_3 group.[8] Therefore, the development of simple methods for the preparation of fluorinated building blocks and their further utilisation for the synthesis of desired R_F-containing heterocyclic compounds are essential. As a continuation of our studies on the synthetic potential of 2-(polyfluoroalkyl)chromones, which turned out to be highly reactive substrates in the reactions with N-,[9] S-,[10] and C-nucleophiles,[11] and owing to the increasing importance of fluorine-containing heterocycles in biology, pharmacology, and industrial applications,[12] we decided to develop a convenient and general synthesis of 3-(polyhaloacyl)chromones as useful precursors of a wide variety of heterocycles with a R_{Hlg} group.[13]

Our new approach to 3-(polyhaloacyl)chromones follows the same design as many older methods in that an appropriately substituted 1,3-diketone is reacted with a one carbon unit of the correct oxidation level. In view of the observation that the readily available diethoxymethyl acetate reacts with 4-(acylacetyl)-1-phenyl-2-pyrazolin-5-ones to yield 5-acyl-4-oxo-1*H*-pyrano[2,3-*c*]pyrazoles,[14] we decided to use diethoxymethyl acetate as an active formylating agent for the synthesis of chromones having a polyhaloacyl group at the 3-position. It should be noted that previously this cyclisation reagent was successfully employed for the preparation of various nitrogen-containing heterocycles, for example purines from the appropriate pyrimidines.[15]

We report here a practical preparation of 3-(polyfluoroacyl)chromones characterised by the use of an excess (6 equiv) of diethoxymethyl acetate as both the formylating agent and solvent, starting from the condensation products of 2-hydroxyacetophenones with R_FCO_2Et. The latter compounds exist in a solution of $CDCl_3$ as a mixture of ring-chain tautomers **1a–l** with the cyclic hemiketal form predominating.[16] The reaction is simply carried out by heating the components for 15 minutes at 140–150 °C, followed by dilution of the resulting mixture with hexane and filtration of the crystalline 3-(polyfluoroacyl)chromones **2a–l** (Table 1). Classical ethyl orthoformate–acetic anhydride mixture failed to give useful results. Compounds **2** were obtained in good yields without the formation of any side products arising from

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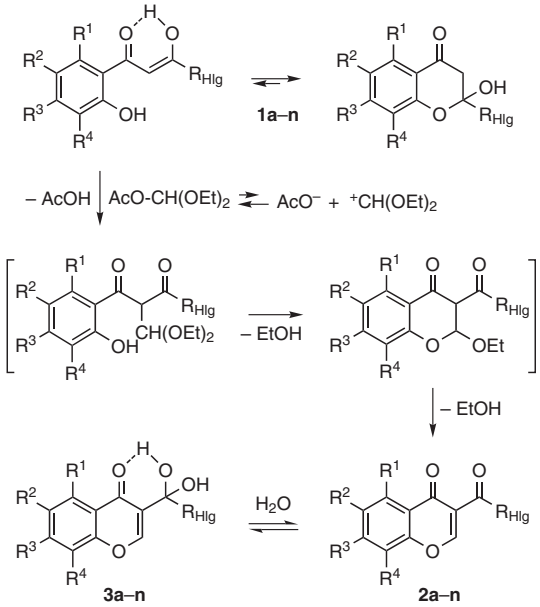
Table 1 Synthesis of 3-(Polyhaloacyl)chromones **2** by Reaction of Chromanones **1** with Diethoxymethyl Acetate

Chromone	R_{Hlg}	R^1	R^2	R^3	R^4	Yield (%)	Mp (°C)
2a	CF_2H	H	H	H	H	77	165–166
2b	CF_2H	H	Me	H	H	62	119–120
2c	CF_2H	H	Cl	H	H	73	133–134
2d	CF_3	H	H	H	H	74	124–125 (125 °C)[6]
2e	CF_3	H	Me	H	H	64	114–115
2f	CF_3	Me	H	Me	H	67	129–130
2g	CF_3	H	NO_2	H	H	81	130–131
2h	CF_3	H	Br	H	Br	53	116–117
2i	$(CF_2)_2H$	H	H	H	H	77	104–105
2j	$(CF_2)_2H$	H	Me	H	H	69	104–105
2k	$(CF_2)_2H$	Me	H	Me	H	73	109–110
2l	$(CF_2)_2H$	H	H	OMe	H	63	105–106
2m	CCl_3	H	H	H	H	30	117–118 (120 °C)[6]
2n	CCl_3	H	H	OMe	H	78	114–115

Michael-type additions onto the C=C bond of the pyrone moiety or dehydration of the starting chromanones **1** to 2-(polyfluoroalkyl)chromones. However, in marked contrast to the 3-formyl- and 3-acetylchromones,[2–5] the chromones obtained in this work were prone to facile and reversible covalent hydrate formation as observed from their ^1H and ^{19}F NMR spectra, which contained two sets of signals. The diagnostic signal for H-2 in chromones **2**, which appeared at 8.5–8.7 ppm, was shifted upfield in hydrates **3** (8.3–8.4 ppm). A plausible pathway leading to the formation of these compounds is outlined in Scheme 1.



Scheme 1

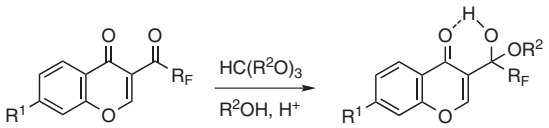
The reaction appears to be general and a variety of substituted 3-(polyfluoroacyl)chromones **2a–l** were obtained by varying the 2-hydroxy-2-(polyfluoroalkyl)chroman-4-ones **1a–l**. It is important that trichloromethyl derivatives **1m** and **1n**[17] also reacted with diethoxymethyl acetate under the same reaction conditions to give 3-(trichloroacetyl)chromones **2m** and **2n** (Table 1). It should be noted that chromones **2** were essentially pure and the yields cited in the Table 1 were determined before recrystallisation. The structures of the chromones **2** was confirmed by elemental analysis, ^1H, ^{19}F NMR, and IR spectroscopy.

We consider the present method a useful and convenient alternative to the existing one.[6] Although in some cases the reaction affords chromones **2** in moderate yields, this approach has advantages with regard to ease of operation and the ready availability of starting materials. The method is experimentally simple and may be of value in R_F-containing building blocks chemistry since chromones **2** may be regarded as latent 1,3-dicarbonyl compounds, having at the 2-position a masked salicyloyl fragment.

On the basis of the elemental analyses and the IR spectra in KBr (the absorption band of the OH group at around 3300–3370 cm^{-1} is absent and two bands of the C=O groups at 1710–1720 and 1650 cm^{-1} are present), it is possible to assume that compounds **2a–c** ($R_F = CF_2H$) and **2i–l** ($R_F = CF_2CF_2H$) in the solid state are pure substances and exist in equilibrium in solution between the non-hydrate **2** and hydrate **3** due to water present in $CDCl_3$ or DMSO-d_6. The ratio of **2** and **3** depends on the number of fluorine atoms present in the R_F group [1–2% of **3** for $R_F = CF_2H$ and 6–8% for $R_F = (CF_2)_2H$]. At the same time, trifluoro- and trichloromethylated products are mix-

tures of **2d–h**, **2m** and **2n** and **3d–h**, **2m** and **2n** as evidenced by their IR spectra (the band corresponding to the OH group at 3300–3370 cm^{-1} and two bands corresponding to the C=O groups at 1720–1740 and 1640–1680 cm^{-1} are present) and the combustion analysis (0.2–0.8 molecule of H_2O). The ^1H and ^{19}F NMR spectra of these compounds in a solution of $CDCl_3$ contained two sets of signals, one of which belonged to chromones **2** (40–80%) and another set was attributed to their hydrates **3** (the amount of **3** present increased with storage). The facile formation of hydrates **3** probably arises from the high hydrophilicity of chromones **2** due to the electrophilic character of the carbonyl carbon atom connected to a polyhaloalkyl substituent and the formation of an intramolecular hydrogen bond between the OH and C=O groups. The facile formation of covalent hydrates from the CF_3-containing β-dicarbonyl compounds is a well-known phenomenon.[18]

As expected, the reaction of chromones **2d** and **2l** with alkyl orthoformates in the corresponding alcohol containing HCl or *p*-TsOH resulted in the formation of hemiketals **4a–c** in 55–66% yields (Scheme 2), but all our attempts to prepare ketals using methanol or ethylene glycol were fruitless. For instance, attempts to obtain the ketals under the same conditions that had previously been used for the acetalisation of 3-formylchromone[19] failed. The failure of the latter reaction possibly results from the destabilisation of the intermediate carbocation by the CF_3 group. In the cases of **4b** and **4c**, the attachment of the ethoxy group to a chiral centre is clearly supported by the ^1H NMR spectra, in which the ethyl group displays an ABX_3 instead of the usual A_2X_3 spin pattern. Note that the starting chromanone **1k** resulted when chromone **2k** was boiled with ethanol in the presence of Et_3N.[19c]



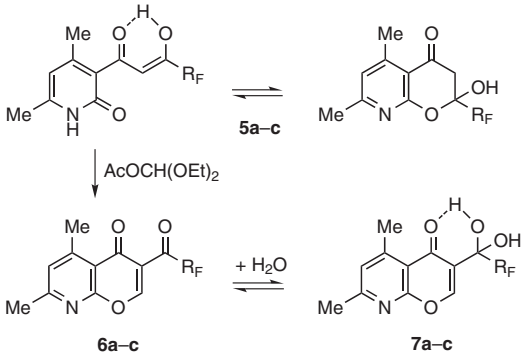
2d,l **4a–c**

$R_F = CF_3$, $R^1 = H$, $R^2 = Me$ (**4a**);
$R_F = CF_3$, $R^1 = H$, $R^2 = Et$ (**4b**);
$R_F = (CF_2)_2H$, $R^1 = MeO$, $R^2 = Et$ (**4c**)

Scheme 2

Extending our studies to the synthesis of hetero analogues of 3-polyfluoroacylchromones **2**, we found that β-diketones **5a–c**, prepared from 3-acetyl-4,6-dimethyl-2-pyridone and R_FCO_2Et in the presence of LiH in dioxane and existing in both $CDCl_3$ and DMSO-d_6 as a mixture of ring-chain tautomers,[20] also undergo this type of reaction with diethoxymethyl acetate under the same experimental conditions (Scheme 3).

Again, the trifluoromethylated azachromone was obtained as a mixture of non-hydrate **6b** and hydrate **7b** (1:1) as can be seen in both the spectral data and elemental anal-



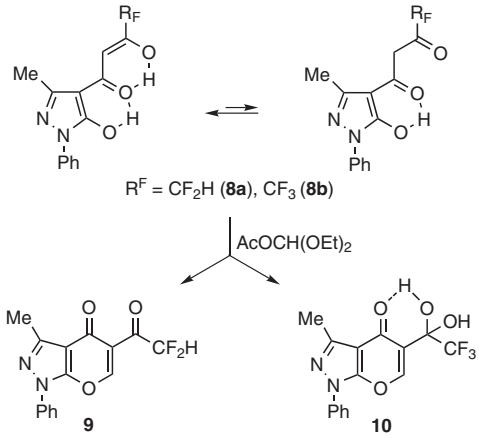
$R_F = CF_2H$ (**a**), CF_3 (**b**), $(CF_2)_2H$ (**c**)

Scheme 3

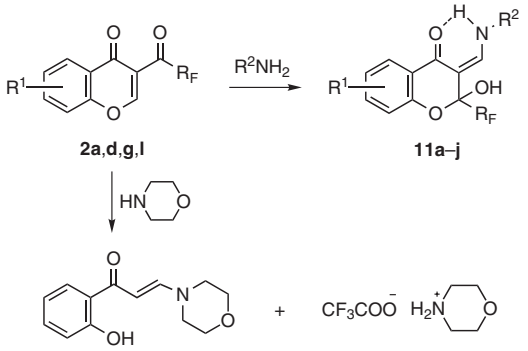
ysis. The ^1H NMR spectrum of this compound showed, in particular, two singlets at 8.56 and 8.35 ppm assigned to the olefinic protons of **6b** and **7b**, respectively. In the ^{19}F NMR spectrum the CF_3 group manifests itself as a singlet at 87.1 and 74.9 ppm for **6b** and **7b**, respectively. The IR spectrum showed strong absorption bands in the range 3400–3210 cm^{-1} (O–H) and 1730–1650 cm^{-1} (C=O) regions.

A Claisen condensation of 4-acetyl-5-hydroxy-3-methyl-1-phenylpyrazole with ethyl di(tri)fluoroacetates in the presence of lithium hydride in THF afforded diketones **8a** and **8b** in 93% and 87% yields, respectively. These compounds, in solution with $CDCl_3$, exist almost exclusively in their keto-enol forms stabilised by two intramolecular hydrogen bonds (Scheme 4). The ^1H NMR spectra of **8a** and **8b** exhibit a singlet corresponding to the olefinic proton at 6.16 and 6.24 ppm and two strongly broadened singlets of the enol (14.4 and 14.5 ppm) and pyrazole (11.7 ppm) hydroxyls. This is in accordance with the data for non-fluorinated analogues of compounds **8a** and **8b** described by Gelin et al.[14] According to the relative integral intensity of the CH_2 group (singlet at 4.14–4.16 ppm), the contents of the diketo form did not exceed 3–4% that is appreciably lower than in the case of 4-acylacetyl-5-hydroxy-1-phenylpyrazoles (6–20%).[14]

When compound **8a** was treated with diethoxymethyl acetate at 140–150 °C for 15 minutes, 5-(difluoroacetyl)-3-methyl-1-phenylpyrano[2,3-*c*]pyrazol-4(1*H*)-one (**9**) was obtained in 64% yield, whereas the analogous reaction with **8b** gave covalent hydrate **10** as the only isolated product (yield 60%). The structure of **10** was confirmed by elemental analysis, IR and ^1H NMR spectra. The IR spectrum in KBr displayed the characteristic absorption band for the pyrone ring carbonyl at 1654 cm^{-1} and a broad band for the hydroxyl groups at 3220 cm^{-1}. The ^1H NMR spectrum of the same sample in DMSO-d_6 (**10** is insoluble in $CDCl_3$) showed two singlets at 8.25 ppm (2 H) and 8.48 ppm (1 H) due to the two OH groups and the H-6 proton, respectively, and the remaining signals correspond to the other protons contained in the substituents.



Scheme 4



Scheme 5

The presence of the electron-withdrawing COR_F group in compounds **2** enhances the electrophilicity of the C-2 atom of the pyrone ring, from the attack of which, as a rule, the interaction of chromones with nucleophilic agents begins.[21,22] Due to this fact, 3-polyfluoroacylchromones and their hetero analogues are promising substrates for the syntheses of new compounds containing the R_F group. Indeed, we have found that the reaction of chromones **2a**, **2d**, **2g** and **2l** with primary amines in methanol at room temperature for two days afforded 3-(alkyl/arylaminomethylene)-2-hydroxy-2-(polyfluoroalkyl)chroman-4-ones **11a–j** in 42–78% yields. Both aliphatic and aromatic amines with electron-donating or electron-withdrawing groups can be employed. The reaction includes the nucleophilic 1,4-addition of the amine with concomitant opening of the pyrone ring and subsequent intramolecular cyclisation of the intermediate at the COR_F group. The driving force for the process is the stabilisation of the enamines **11** by a hydrogen bond between the pyranone carbonyl oxygen and the hydrogen of the NH group (Scheme 5). Unlike primary amines, morpholine reacted with **2d** under the same reaction conditions to give a 1:1 mixture of the previously known aminoenone, *trans*-1-(2-hydroxyphenyl)-3-morpholinoprop-2-en-1-one[23] and morpholinium trifluoroacetate in 74% yield. In this case, detrifluoroacetylation took place as an unwanted reaction.

It should be noted that the reaction between equimolar quantities of 3-formylchromone and a primary aromatic amine leads to a mixture of the 3-(aryliminomethyl)chromone and 2-arylamino-3-(arylaminomethylene)chroman-4-one, making the isolation of pure compounds difficult.[24] This different behaviour is not unexpected, considering that the R_F group complicates the dehydration stage. Recently, 3-(arylaminomethylene)-2-hydroxychroman-4-ones were prepared by the acid-catalysed reaction of 3-formylchromones with aromatic amino carboxylic acids in benzene or toluene.[25]

The structures of compounds **11a–j** are consistent with the IR, ^1H and ^{19}F NMR spectra. The IR spectra of **11a–j** showed absorption bands in two ranges 3290–3130 and 1650–1600 cm^{-1} due to the OH and NH groups and the aminoenone fragment. A characteristic feature of the ^1H NMR spectra in DMSO-d_6 is the appearance of one sin-

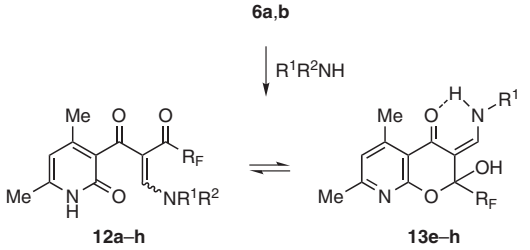
Table 2 Reaction of 3-(Polyfluoroacyl)chromones **2** with Primary Amines

Compd	R_F	R^1	R^2	Yield (%)	Mp (°C)
11a	CF_2H	H	Bn	61	149–150
11b	CF_2H	H	*p*-$MeOC_6H_4$	75	178–179
11c	CF_3	H	*c*-C_6H_{11}	50	133–134
11d	CF_3	H	Bn	42	122–123
11e	CF_3	H	Ph	76	143–144
11f	CF_3	H	*p*-MeC_6H_4	62	184–185
11g	CF_3	H	*p*-$MeOC_6H_4$	77	194–195
11h	CF_3	H	*p*-$NO_2C_6H_4$	68	213–214
11i	CF_3	6-NO_2	Ph	61	221–222
11j	$(CF_2)_2H$	7-OMe	*p*-$MeOC_6H_4$	78	182–183

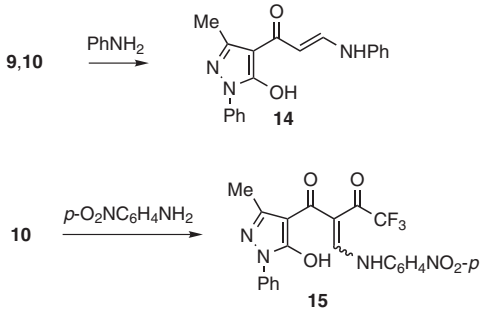
glet at 8.3–9.6 ppm for the OH proton (4.0–4.2 ppm in $CDCl_3$), and two AX doublets (J_{AX} = 12.6–13.3 Hz) at 7.8–8.1 and 12.5–12.6 ppm for the =CH and NH protons, respectively. The addition of CD_3CO_2D to a solution of **11e** in DMSO-d_6 results in the disappearance of the signals due to OH and NH protons, whereas the doublet at 8.00 ppm (=CH) turns into a singlet.

Since the key step of the transformation **2**→**11** is the interaction of primary amines with the C-2 atom, we were interested in introducing 8-aza-5,7-dimethyl-3-(polyfluoroacyl)chromones **6a** and **6b** into this reaction. In this case, opening of the pyrone ring results in the appearance of the amide-type oxygen atom with decreased nucleophilicity instead of the phenol OH group. This allowed us to expect the isolation of open-chained products. In fact, chromone **6a** in THF or MeOH reacted with isopropylamine and secondary cyclic amines (pyrrolidine, piperidine and morpholine) to give acyclic compounds **12a–d** as the only geometric isomer (configuration of the double bond was not determined); no detectable amount of the cyclic isomer was found in the ^{1}H NMR spectra of these compounds in DMSO-d_6. However, the reactions of **6a** with aromatic amines (aniline and *p*-anisidine) led to the adducts as a mixture of ring-chain isomers (4–8% of cyclic form **13e** and **13f** in DMSO-d_6). It is interesting that an increase from two to three fluorine atoms in a polyfluoroacyl group resulted in an increase in the cyclic isomer, for **13g** and **13h** up to 56–64%; this fact indicated that the CF_3 group is more capable of stabilising hemiketal **13** (Scheme 6). In the crystalline state, compounds **12a–h** exist in a cyclic hemiketal form **13** as evidenced by their IR spectra recorded in KBr (the absorption band of the R_FCO group at around 1700 cm^{-1} is absent and bands in the two ranges 3280–2640 and 1660–1580 cm^{-1} due to the OH and NH groups and the aminoenone fragment are present). The products **12** appeared as colourless or yellow compounds decomposing near their melting points.

It was also found that upon reaction with aniline, pyranopyrazoles **9** and **10** lost the di(tri)fluoroacetyl group and gave aminoenone **14** as a mixture of *E*- and *Z*-isomers in a ratio of 9:1 (J_{trans} = 12.5 Hz, J_{cis} = 7.9 Hz), while the reaction of **10** with less basic *p*-nitroaniline ceased at the pyrone ring-opening step, resulting in trifluoroacetylated acyclic compound **15** (DMSO-d_6) in 72% yield (Scheme 7). On the basis of the elemental analysis data and a broadened singlet at 3.6 ppm in the ^{1}H NMR spectrum, one can conclude that this compound exists as a hydrate.



Scheme 6



Scheme 7

Thus, the reaction of 3-(polyfluoroacyl)chromones and their hetero analogues with amines starts from attack at C-2 of the pyrone ring and affords, depending on the nature of the reactant and substrate, compounds of two types: R_FCO-containing aminoenones, which exist only in a cyclic form in a solid state, and aminoenones without the R_FCO group.

In conclusion, we have developed an easy and convenient one-step synthesis of 3-(polyhaloacyl)chromones and

Table 3 Reaction of 8-Aza-5,7-dimethyl-3-(polyfluoroacyl)chromones **6a** and **6b** with Amines

12	R_F	R^1	R^2	Ratio of **12/13**	Yield (%)	Mp (°C)
a	CF_2H	*i*-Pr	H	100:0	72	186–187
b	CF_2H	$(CH_2)_4$		100:0	54	221–222
c	CF_2H	$(CH_2)_5$		100:0	74	216–217
d	CF_2H	$(CH_2)_2O(CH_2)_2$		100:0	51	217–218
e	CF_2H	*p*-$MeOC_6H_4$	H	96:4	88	232–234
f	CF_2H	Ph	H	92:8	86	234–235
g	CF_3	*p*-$MeOC_6H_4$	H	44:56	76	233–235
h	CF_3	Ph	H	36:64	52	182–183

their hetero analogues, starting from readily obtainable 2-hydroxy-2-(polyhaloalkyl)chroman-4-ones and commercially available diethoxymethyl acetate. These compounds are of much interest as reactive precursors in the synthesis of other useful organic materials with polyfluoroalkyl and trichloromethyl groups.

Table 4 Analytical and Spectral Data for 3-(Polyhaloacyl)chromones **2a**–**n**[a]

Chromone/ Hydrate	Molecular formula	IR (KBr, cm^{-1})	^1H NMR ($CDCl_3$) δ, *J* (Hz)
2a[b,c]	$C_{11}H_6F_2O_3$	3076, 1711, 1654, 1614, 1560	6.97 (t, $^2J_{H,F}$ = 53.3, 1 H, CF_2H), 7.54 (t, ^oJ = 7.6, 1 H, H-6), 7.57 (d, ^oJ = 8.4, 1 H, H-8), 7.79 (ddd, ^oJ = 8.6, 7.2, ^mJ = 1.6, 1 H, H-7), 8.30 (dd, ^oJ = 8.0, ^mJ = 1.6, 1 H, H-5), 8.68 (s, 1 H, H-2)
3a (1%)			5.47 (s, 2 H, 2 × OH), 5.78 (t, $^2J_{H,F}$ = 56.1, 1 H, CF_2H), 8.35 (s, 1 H, H-2)
2b	$C_{12}H_8F_2O_3$	3063, 1718, 1654, 1620, 1600, 1561	2.50 (s, 3 H, Me), 6.97 (t, $^2J_{H,F}$ = 53.3, 1 H, CF_2H), 7.46 (d, ^oJ = 8.5, 1 H, H-8), 7.58 (dd, ^oJ = 8.5, ^mJ = 2.1, 1 H, H-7), 8.07 (br d, ^mJ = ca. 1.5, 1 H, H-5), 8.65 (s, 1 H, H-2)
3b (2%)			2.47 (s, 3 H, Me), 5.51 (s, 2 H, 2 × OH), 5.77 (t, $^2J_{H,F}$ = 56.1, 1 H, CF_2H), 8.32 (s, 1 H, H-2)
2c	$C_{11}H_5ClF_2O_3$	3085, 1717, 1654, 1610, 1560	6.93 (t, $^2J_{H,F}$ = 53.2, 1 H, CF_2H), 7.54 (d, ^oJ = 8.9, 1 H, H-8), 7.73 (dd, ^oJ = 8.9, ^mJ = 2.6, 1 H, H-7), 8.25 (d, ^mJ = 2.6, 1 H, H-5), 8.66 (s, 1 H, H-2)
3c (1%)			5.31 (s, 2 H, 2 × OH), 5.80 (t, $^2J_{H,F}$ = 56.0, 1 H, CF_2H), 8.34 (s, 1 H, H-2)
2d[d]	$C_{11}H_5F_3O_3 \cdot 0.5H_2O$	3343, 1640, 1599, 1573	7.50–7.58 (m, 2 H, H-6, H-8), 7.79 (ddd, ^oJ = 8.6, 7.0, ^mJ = 1.7, 1 H, H-7), 8.30 (dd, ^oJ = 8.0, ^mJ = 1.7, 1 H, H-5), 8.62 (s, 1 H, H-2)
3d (50%)			6.06 (s, 2 H, 2 × OH), 7.50–7.58 (m, 2 H, H-6, H-8), 7.78 (ddd, ^oJ = 8.6, 7.0, ^mJ = 1.7, 1 H, H-7), 8.26 (dd, ^oJ = 8.0, ^mJ = 1.7, 1 H, H-5), 8.40 (s, 1 H, H-2)
2e	$C_{12}H_7F_3O_3$	3309, 3059, 1718, 1664, 1635, 1601, 1558	2.49 (s, 3 H, Me), 7.44 (d, ^oJ = 8.6, 1 H, H-8), 7.57 (ddq, ^oJ = 8.6, ^mJ = 2.0, $^4J_{H,CH3}$ = 0.6, 1 H, H-7), 8.07 (dq, ^mJ = 2.0, $^4J_{H,CH3}$ = 0.6, 1 H, H-5), 8.59 (s, 1 H, H-2)
3e (30%)			2.49 (s, 3 H, Me), 6.16 (s, 2 H, 2 × OH), 7.45 (d, ^oJ = 8.6, 1 H, H-8), 7.59 (ddq, ^oJ = 8.6, ^mJ = 2.0, ^4J = 0.6, 1 H, H-7), 8.02 (dq, ^mJ = 2.0, ^4J = 0.6, 1 H, H-5), 8.37 (s, 1 H, H-2)
2f	$C_{13}H_9F_3O_3 \cdot 0.8H_2O$	3337, 1638, 1584, 1559, 1517	2.45 (s, 3 H, Me), 2.83 (s, 3 H, Me), 7.06 (s, 1 H, H-6), 7.15 (s, 1 H, H-8), 8.44 (s, 1 H, H-2)
3f (65%)			2.45 (s, 3 H, Me), 2.80 (s, 3 H, Me), 6.24 (s, 2 H, 2 × OH), 7.03 (s, 1 H, H-6), 7.15 (s, 1 H, H-8), 8.24 (s, 1 H, H-2)
2g	$C_{11}H_4F_3NO_5 \cdot 0.25H_2O$	3352, 3104, 3058, 1717, 1680, 1630, 1553, 1536	7.76 (dd, ^oJ = 9.2, ^pJ = 0.3, 1 H, H-8), 8.61 (dd, ^oJ = 9.2, ^mJ = 2.8, 1 H, H-7), 8.66 (s, 1 H, H-2), 9.15 (dd, ^mJ = 2.8, ^pJ = 0.3, 1 H, H-5)
3g (45%)			5.82 (s, 2 H, 2 × OH), 7.75 (dd, ^oJ = 9.2, ^pJ = 0.3, 1 H, H-8), 8.45 (s, 1 H, H-2), 8.61 (dd, ^oJ = 9.2, ^mJ = 2.8, 1 H, H-7), 9.12 (dd, ^mJ = 2.8, ^pJ = 0.3, 1 H, H-5)
2h	$C_{11}H_3Br_2F_3O_3 \cdot 0.5H_2O$	3369, 1638, 1589, 1555	8.11 (d, ^mJ = 2.3, 1 H, H-7), 8.36 (d, ^mJ = 2.3, 1 H, H-5), 8.67 (s, 1 H, H-2)
3h (57%)			5.79 (s, 2 H, 2 × OH), 8.13 (d, ^mJ = 2.3, 1 H, H-7), 8.32 (d, ^mJ = 2.3, 1 H, H-5), 8.47 (s, 1 H, H-2)
2i[e,f]	$C_{12}H_6F_4O_3$	3077, 1718, 1650, 1614, 1561	6.80 (tt, $^2J_{H,F}$ = 53.3, $^3J_{H,F}$ = 5.8, 1 H, CF_2CF_2H,), 7.54 (ddd, ^oJ = 8.0, 7.2, ^mJ = 1.0, 1 H, H-6), 7.57 (ddd, ^oJ = 8.5, ^mJ = 1.0, ^pJ = 0.4, 1 H, H-8), 7.79 (ddd, ^oJ = 8.6, 7.2, ^mJ = 1.7, 1 H, H-7), 8.27 (ddd, ^oJ = 8.0, ^mJ = 1.7, ^pJ = 0.4, 1 H, H-5), 8.55 (s, 1 H, H-2)
3i (6%)			6.28 (tt, $^2J_{H,F}$ = 53.2, $^3J_{H,F}$ = 6.2, 1 H, CF_2CF_2H), 6.31 (s, 2 H, 2 × OH), 7.51 (ddd, ^oJ = 8.0, 7.2, ^mJ = 1.0, 1 H, H-6), 7.57 (dd, ^oJ = 8.5, ^mJ = 1.0, 1 H, H-8), 7.79 (ddd, ^oJ = 8.6, 7.2, ^mJ = 1.7, 1 H, H-7), 8.23 (dd, ^oJ = 8.0, ^mJ = 1.7, 1 H, H-5), 8.37 (s, 1 H, H-2)

Table 4 Analytical and Spectral Data for 3-(Polyhaloacyl)chromones **2a–n**[a] (continued)

Chromone/ Hydrate	Molecular formula	IR (KBr, cm^{-1})	^1H NMR ($CDCl_3$) δ, *J* (Hz)
2j	$C_{13}H_8F_4O_3$	3064, 1715, 1648, 1619, 1601, 1560	2.50 (s, 3 H, Me), 6.81 (tt, $^2J_{H,F}$ = 53.3, $^3J_{H,F}$ = 5.8, 1 H, CF_2CF_2H), 7.46 (d, ^oJ = 8.5, 1 H, H-8), 7.59 (ddq, ^oJ = 8.5, ^mJ = 2.3, $^4J_{H,CH3}$ = 0.6, 1 H, H-7), 8.05 (br s, 1 H, H-5), 8.53 (s, 1 H, H-2)
3j (6%)			6.27 (s, 2 H, 2 × OH), 6.28 (tt, $^2J_{H,F}$ = 53.2, $^3J_{H,F}$ = 6.2, 1 H, CF_2CF_2H), 8.02 (br s, 1 H, H-5), 8.35 (s, 1 H, H-2)
2k	$C_{14}H_{10}F_4O_3$	3094, 1720, 1650, 1621, 1599, 1554	2.45 (s, 3 H, Me), 2.80 (s, 3 H, Me), 6.78 (tt, $^2J_{H,F}$ = 53.3, $^3J_{H,F}$ = 5.8, 1 H, CF_2CF_2H), 7.06 (s, 1 H, Ar), 7.15 (s, 1 H, Ar), 8.36 (s, 1 H, H-2)
3k (8%)			2.45 (s, 3 H, Me), 2.78 (s, 3 H, Me), 6.27 (tt, $^2J_{H,F}$ = 53.2, $^3J_{H,F}$ = 6.3, 1 H, CF_2CF_2H), 6.41 (s, 2 H, 2 × OH), 7.03 (s, 1 H, Ar), 7.15 (s, 1 H, Ar), 8.22 (s, 1 H, H-2)
2l	$C_{13}H_8F_4O_4$	3077, 1711, 1657, 1621, 1557, 1502	3.94 (s, 3 H, OMe), 6.83 (tt, $^2J_{H,F}$ = 53.3, $^3J_{H,F}$ = 5.8, 1 H, CF_2CF_2H,), 6.93 (d, ^oJ = 2.3, 1 H, H-8), 7.07 (dd, ^oJ = 8.9, ^mJ = 2.3, 1 H, H-6), 8.16 (d, ^oJ = 8.9, 1 H, H-5), 8.47 (s, 1 H, H-2)
3l (8%)			3.93 (s, 3 H, OMe), 6.36 (s, 2 H, 2 × OH), 6.28 (tt, $^2J_{H,F}$ = 53.2, $^3J_{H,F}$ = 6.1, 1 H, CF_2CF_2H), 6.90 (d, ^oJ = 2.3, 1 H, H-8), 7.03 (dd, ^oJ = 8.9, ^mJ = 2.3, 1 H, H-6), 8.11 (d, ^oJ = 8.9, 1 H, H-5), 8.28 (s, 1 H, H-2)
2m	$C_{11}H_5Cl_3O_3$	3202, 3081, 1742, 1643, 1618, 1569	7.51 (ddd, ^oJ = 8.0, 7.2, ^mJ = 1.0, 1 H, H-6), 7.54 (d, ^oJ = 8.6, 1 H, H-8), 7.77 (ddd, ^oJ = 8.6, 7.2, ^mJ = 1.7, 1 H, H-7), 8.28 (dd, ^oJ = 8.0, ^mJ = 1.7, 1 H, H-5), 8.57 (s, 1 H, H-2)
3m (20%)			6.66 (s, 2 H, 2 × OH), 7.52 (m, 1 H, H-6), 7.57 (d, ^oJ = 8.5, 1 H, H-8), 7.79 (ddd, ^oJ = 8.7, 7.2, ^mJ = 1.7, 1 H, H-7), 8.27 (dd, ^oJ = 8.0, ^mJ = 1.7, 1 H, H-5), 8.60 (s, 1 H, H-2)
2n	$C_{12}H_7Cl_3O_4$	3355, 1743, 1635, 1581, 1566, 1507	3.93 (s, 3 H, OMe), 6.90 (d, ^oJ = 2.4, 1 H, H-8), 7.05 (dd, ^oJ = 8.9, ^mJ = 2.4, 1 H, H-6), 8.17 (d, ^oJ = 8.9, 1 H, H-5), 8.48 (s, 1 H, H-2)
3n (29%)			3.94 (s, 3 H, OMe), 6.78 (s, 2 H, 2 × OH), 6.92 (d, ^oJ = 2.4, 1 H, H-8), 7.07 (dd, ^oJ = 8.9, ^mJ = 2.4, 1 H, H-6), 8.15 (d, ^oJ = 8.9, 1 H, H-5), 8.51 (s, 1 H, H-2)

[a] Elemental analyses were within allowed error, C ± 0.35; H ± 0.39.
[b] ^{13}C NMR ($CDCl_3$): δ = 109.03 (t, $^1J_{C,F}$ = 247.6 Hz), 118.45, 120.25, 124.74, 126.50, 126.97, 135.10, 155.84, 162.85, 174.42, 186.51 (t, $^2J_{C,F}$ = 25.6 Hz).
[c] **2a** ^{19}F NMR ($CDCl_3$): δ = 30.81 (d, $^2J_{F,H}$ = 53.3 Hz, HCF_2); **3a** ^{19}F NMR ($CDCl_3$, 2%): δ = 28.72 (d, $^2J_{F,H}$ = 56.1 Hz, HCF_2).
[d] **2d** ^{19}F NMR ($CDCl_3$): δ = 86.93 (s, CF_3); **3d** ^{19}F NMR ($CDCl_3$, 50%): δ = 74.85 (s, CF_3).
[e] ^{13}C NMR ($CDCl_3$): δ = 109.07 (tt, $^1J_{C,F}$ = 252.0 Hz, $^2J_{C,F}$ = 30.5 Hz), 110.54 (tt, $^1J_{C,F}$ = 262.1 Hz, $^2J_{C,F}$ = 27.4 Hz), 118.40, 120.85, 124.61, 126.39, 127.03, 135.17, 155.69, 162.30 (t, $^4J_{C,F}$ = 2.2 Hz), 173.69, 185.58 (t, $^2J_{C,F}$ = 29.3 Hz).
[f] **2i** ^{19}F NMR ($CDCl_3$): δ = 24.06 (dt, $^2J_{H,F}$ = 53.3 Hz, $^3J_{F,F}$ = 7.3 Hz HCF_2CF_2), 38.73 (td, $^3J_{F,F}$ = 7.3 Hz, $^3J_{F,H}$ = 5.8 Hz, HCF_2CF_2); **3i** ^{19}F NMR ($CDCl_3$, 10%): δ =25.39 (dt, $^2J_{F,H}$ = 53.1 Hz, $^3J_{F,F}$ = 7.7 Hz, HCF_2CF_2, $^2J_{F,H}$ = 53.1 Hz, $^3J_{F,F}$ = 7.7 Hz), 30.78 (q, $^3J_{F,F}$ = $^3J_{F,H}$ = ca. 7.0 Hz, HCF_2CF_2).

Table 5 Analytical and Spectral Data for Compounds **11a–j** and **12a–h**[a]

Compd	Molecular formula	IR (KBr, cm^{-1})	^1H NMR (DMSO-d_6) δ, *J* (Hz)
11a[b]	$C_{18}H_{15}F_2NO_3$	3240, 1643, 1609, 1594, 1540	4.12 (br s, 1 H, OH), 4.41 (d, *J* = 6.1, 2 H, CH_2), 5.70 (t, $^2J_{H,F}$ = 56.2, 1 H, CF_2H), 6.94 (dd, ^oJ = 8.2, ^mJ = 0.9, 1 H, H-8), 7.05 (ddd, ^oJ = 7.8, 7.2, ^mJ = 0.9, 1 H, H-6), 7.23–7.43 (m, 7 H, Ph, H-7, =CH), 7.86 (dd, ^oJ = 7.8, ^mJ = 1.7, 1 H, H-5), 11.16 (br s, 1 H, NH)
11b	$C_{18}H_{15}F_2NO_4$	3287, 1637, 1604, 1587, 1544, 1516	3.77 (s, 3 H, OMe), 6.07 (t, $^2J_{H,F}$ = 55.4, 1 H, CF_2H), 6.99 (dd, ^oJ = 8.3, ^mJ = 1.0, 1 H, H-8), 7.00 (d, 2 H, H-2′, H-6′), 7.08 (ddd, ^oJ = 9.0, 1 H, H-6, ^oJ = 7.8, 7.3, ^mJ = 1.0), 7.34 (d, ^oJ = 9.0, 2 H, H-3′, H-5′), 7.48 (ddd, ^oJ = 8.3, 7.3, ^mJ = 1.7, 1 H, H-7), 7.79 (dd, ^oJ = 7.8, ^mJ = 1.7, 1 H, H-5), 7.82 (d, *J* = 12.8, 1 H, =CH), 8.33 (s, 1 H, OH), 12.57 (d, *J* = 12.8, 1 H, NH)

Table 5 Analytical and Spectral Data for Compounds **11a–j** and **12a–h**[a] (continued)

Compd	Molecular formula	IR (KBr, cm^{-1})	^1H NMR (DMSO-d_6) δ, *J* (Hz)
11c[b]	$C_{17}H_{18}F_3NO_3 \cdot 0.25H_2O$	3200, 1646, 1610, 1596, 1547	1.30–1.97 [m, 10 H, $(CH_2)_5$], 3.12–3.22 (m, 1 H, CHN), 4.03 (br s, 1 H, OH), 6.95 (dd, ^oJ = 8.2, ^mJ = 1.0, 1 H, H-8), 7.07 (ddd, ^oJ = 7.8, 7.3, ^mJ = 1.0, 1 H, H-6), 7.39 (ddd, ^oJ = 8.2, 7.3, ^mJ = 1.7, 1 H, H-7), 7.47 (d, *J* = 13.4, 1 H, =CH), 7.88 (dd, ^oJ = 7.8, ^mJ = 1.7, 1 H, H-5), 11.10 (br s, 1 H, NH)
11d[b]	$C_{18}H_{14}F_3NO_3 \cdot 0.5H_2O$	3251, 1644, 1610, 1594, 1544	4.19 (br s, 1 H, OH), 4.43 (d, *J* = 6.1, 1 H, CH_2), 6.97 (dd, ^oJ = 8.3, ^mJ = 1.0, 1 H, H-8), 7.08 (ddd, ^oJ = 7.8, 7.3, ^mJ = 1.0, 1 H, H-6), 7.22–7.26 (m, 2 H, H-2′, H-6′), 7.29–7.39 (m, 3 H, H-3′, H-4′, H-5′), 7.41 (ddd, ^oJ = 8.3, 7.3, ^mJ = 1.7, 1 H, H-7), 7.45 (d, *J* = 14.0, 1 H, =CH), 7.88 (dd, ^oJ = 7.8, ^mJ = 1.7, 1 H, H-5), 11.21 (br s, 1 H, NH)
11e[c,d]	$C_{17}H_{12}F_3NO_3$	3228, 1639, 1599, 1588, 1548	7.07 (dd, ^oJ = 8.3, ^mJ = 1.0, 1 H, H-8), 7.15 (ddd, ^oJ = 7.7, 7.3, ^mJ = 1.0, 1 H, H-6), 7.18–7.23 (m, 1 H, H-4′), 7.40–7.46 (m, 4 H, H-2′, H-3′, H-5′, H-6′), 7.55 (ddd, ^oJ = 8.3, 7.3, ^mJ = 1.7, 1 H, H-7), 7.83 (dd, ^oJ = 7.7, ^mJ = 1.7, 1 H, H-5), 8.00 (d, *J* = 12.9, 1 H, =CH), 9.12 (s, 1 H, OH), 12.53 (d, *J* = 12.9, 1 H, NH)
11f	$C_{18}H_{14}F_3NO_3$	3254, 1642, 1604, 1587, 1545, 1519	2.30 (s, 3 H, Me), 7.06 (d, ^oJ = 8.2, ^mJ = 1.0, 1 H, H-8), 7.14 (ddd, ^oJ = 7.8, 7.3, ^mJ = 1.0, 1 H, H-6), 7.24 (d, ^oJ = 8.4, 2 H, H-2′, H-6′), 7.31 (d, ^oJ = 8.4, 2 H, H-3′, H-5′), 7.53 (ddd, ^oJ = 8.3, 7.3, ^mJ = 1.7, 1 H, H-7), 7.82 (dd, ^oJ = 7.8, ^mJ = 1.7, 1 H, H-5), 7.96 (d, *J* = 12.9, 1 H, =CH), 9.08 (s, 1 H, OH), 12.55 (d, *J* = 12.9, 1 H, NH)
11g	$C_{18}H_{14}F_3NO_4$	3278, 1639, 1602, 1587, 1544, 1516	3.77 (s, 3 H, OMe), 7.00 (d, ^oJ = 9.0, 2 H, H-2′, H-6′), 7.05 (dd, ^oJ = 8.3, ^mJ = 1.0, 1 H, H-8), 7.13 (ddd, ^oJ = 7.8, 7.3, ^mJ = 1.0, 1 H, H-6), 7.37 (d, ^oJ = 9.0, 2 H, H-3′, H-5′), 7.53 (ddd, ^oJ = 8.3, 7.3, ^mJ = 1.7, 1 H, H-7), 7.81 (dd, ^oJ = 7.8, ^mJ = 1.7, 1 H, H-5), 7.89 (d, *J* = 13.0, 1 H, =CH), 9.05 (s, 1 H, OH), 12.60 (d, *J* = 13.0, 1 H, NH)
11h	$C_{17}H_{11}F_3N_2O_5 \cdot 0.5H_2O$	3130, 1639, 1585, 1564, 1524	7.10 (dd, ^oJ = 8.3, ^mJ = 1.0, 1 H, H-8), 7.18 (ddd, ^oJ = 7.8, 7.3, ^mJ = 1.0, 1 H, H-6), 7.59 (ddd, ^oJ = 8.3, 7.3, ^mJ = 1.7, 1 H, H-7), 7.69 (d, ^oJ = 9.2, 2 H, H-2′, H-6′), 7.85 (dd, ^oJ = 7.8, ^mJ = 1.7, 1 H, H-5), 8.09 (d, *J* = 12.6, 1 H, =CH), 8.27 (d, ^oJ = 9.2, 2 H, H-3′, H-5′), 9.28 (s, 1 H, OH), 12.47 (d, *J* = 12.6, 1 H, NH)
11i	$C_{17}H_{11}F_3N_2O_5$	3316, 1642, 1618, 1600, 1588, 1560, 1521	7.25 (t, ^oJ = 6.8, 1 H, H-4′), 7.35 (d, ^oJ = 9.0, 1 H, H-8), 7.44–7.50 (m, 4 H, H-2′, H-3′, H-5′, H-6′), 8.10 (d, *J* = 13.3, 1 H, =CH), 8.38 (dd, ^oJ = 9.0, ^mJ = 2.9, 1 H, H-7), 8.58 (d, ^mJ = 2.9, 1 H, H-5), 9.61 (s, 1 H, OH), 12.59 (d, *J* = 13.3, 1 H, NH)
11j	$C_{20}H_{17}F_4NO_5$	3208, 1644, 1607, 1584, 1535, 1518	3.76 (s, 3 H, OMe), 3.82 (s, 3 H, OMe), 6.52 (d, ^mJ = 2.4, 1 H, H-8), 6.69 (tdd, $^2J_{H,F}$ = 52.2, $^3J_{H,F}$ = 5.9, 7.4, 1 H, CF_2CF_2H), 6.69 (dd, ^oJ = 8.7, ^mJ = 2.4, 1 H, H-6), 6.99 (d, ^oJ = 9.0, 2 H, H-2′, H-6′), 7.31 (d, ^oJ = 9.0, 2 H, H-3′, H-5′), 7.71 (d, ^oJ = 8.7, 1 H, H-5), 7.75 (dd, *J* = 12.8, 1.3, 1 H, =CH), 8.94 (d, *J* = 4.1, 1 H, OH), 12.47 (d, *J* = 12.8, 1 H, NH)
12a	$C_{15}H_{18}F_2N_2O_3$	3220–2650, 1656, 1636, 1592, 1541	1.21 (d, *J* = 6.3, 6 H, 2 × Me), 1.98 (s, 3 H, Me), 2.16 (s, 3 H, Me), 3.79 (d sept, $J_{CH,NH}$ = 7.3, *J* = 6.3, 1 H, CH), 5.96 (s, 1 H, Py), 6.84 (t, $^2J_{H,F}$ = 54.8, 1 H, CF_2H), 7.75 (br d, *J* = ca. 12.0, 1 H, =CH,), 10.77 (br s, 1 H, NH), 11.68 (br s, 1 H, PyNH)
12b	$C_{16}H_{18}F_2N_2O_3$	3280–2650, 1660, 1635, 1600, 1575	1.85 (quint, *J* = 6.8, 2 H, CH_2), 1.95 (quint, *J* = 6.8, 2 H, CH_2), 2.00 (s, 3 H, Me), 2.15 (s, 3 H, Me), 2.88 (t, *J* = 6.8, 2 H, CH_2), 3.70 (t, *J* = 6.8, 2 H, CH_2), 5.93 (s, 1 H, Py), 6.61 (t, $^2J_{H,F}$ = 54.7, 1 H, CF_2H), 7.66 (s, 1 H, =CH), 11.58 (br s, 1 H, PyNH)
12c	$C_{17}H_{20}F_2N_2O_3$	3280–2650, 1659, 1636, 1602, 1579	1.60–1.65 (br s, 6 H, 3 × CH_2), 2.02 (s, 3 H, Me), 2.15 (s, 3 H, Me), 3.10–3.24 (br s, 2 H, CH_2), 3.55–3.65 (m, 2 H, CH_2), 5.93 (s, 1 H, Py), 6.64 (t, $^2J_{H,F}$ = 54.8, 1 H, CF_2H), 7.59 (s, 1 H, =CH), 11.59 (br s, 1 H, PyNH)
12d	$C_{16}H_{18}F_2N_2O_4$	3280–2650, 1659, 1633, 1608, 1575	2.03 (s, 3 H, Me), 2.15 (s, 3 H, Me), 3.30 (s, 4 H, 2 × CH_2), 3.67–3.71 (m, 4 H, 2 × CH_2), 5.94 (s, 1 H, Py), 6.63 (t, $^2J_{H,F}$ = 54.6, 1 H, CF_2H), 7.65 (s, 1 H, =CH), 11.62 (br s, 1 H, PyNH)

Table 5 Analytical and Spectral Data for Compounds **11a–j** and **12a–h**[a] (continued)

Compd	Molecular formula	IR (KBr, cm^{-1})	^1H NMR (DMSO-d_6) δ, *J* (Hz)
12e	$C_{19}H_{18}F_2N_2O_4 \cdot 0.5H_2O$	3120–2660, 1630, 1581, 1550, 1513	Major isomer (80%): 2.05 (s, 3 H, Me), 2.17 (s, 3 H, Me), 3.76 (s, 3 H, OMe), 6.01 (s, 1 H, Py), 6.92 (t, $^2J_{H,F}$ = 54.1, 1 H, CF_2H), 6.98–7.00 (m, 2 H, Ar), 7.28–7.30 (m, 2 H, Ar), 7.93 (br s, 1 H, =CH), 11.80 (br s, 1 H, PyNH), 12.26 (br s, 1 H, NH) Minor isomer (16%): 2.03 (s, 3 H, Me), 2.16 (s, 3 H, Me), 3.76 (s, 3 H, OMe), 5.93 (s, 1 H, Py), 7.0 (m, 2 H, Ar), 7.5 (br s, 2 H, Ar), 8.35 (br s, 1 H, =CH), 11.5 (br s, 1 H, PyNH), 12.6 (br s, 1 H, NH)
12f	$C_{18}H_{16}F_2N_2O_3 \cdot 0.5H_2O$	3130–2670, 1640, 1618, 1582, 1545, 1498	Major isomer (75%): 2.07 (s, 3 H, Me), 2.18 (s, 3 H, Me), 6.03 (s, 1 H, Py), 6.93 (t, $^2J_{H,F}$ = 54.1, 1 H, CF_2H), 7.25–7.50 (m, 5 H, Ph), 8.04 (d, *J* = 13.9, 1 H, =CH), 11.83 (br s, 1 H, PyNH), 12.24 (d, *J* = 14.0, 1 H, NH) Minor isomer (17%): 2.01 (s, 3 H, Me), 2.15 (s, 3 H, Me), 5.91 (s, 1 H, Py), 6.84 (t, $^2J_{H,F}$ = 53.4, 1 H, CF_2H), 7.4–7.6 (m, 5 H, Ph), 8.43 (d, *J* = 12.0, 1 H, =CH), 11.55 (br s, 1 H, PyNH), 12.59 (d, *J* = 12.3, 1 H, NH)
13f (8%)			2.37 (s, 3 H, Me), 2.67 (s, 3 H, Me), 6.10 (t, $^2J_{H,F}$ = 55.4, 1 H, CF_2H), 6.87 (s, 1 H, Py), 7.4 (m, 5 H, Ph), 7.86 (d, *J* = 12.8, 1 H, =CH), 12.33 (d, *J* = 12.7, 1 H, NH)
12g[e]	$C_{19}H_{17}F_3N_2O_4 \cdot 0.5H_2O$	3130–2670, 1624, 1585, 1558, 1514	2.08 (s, 3 H, Me), 2.16 (s, 3 H, Me), 3.78 (s, 3 H, OMe), 5.96 (br s, 1 H, Py), 7.01 (m, 2 H, Ar), 7.44 (br s, 2 H, Ar), 7.9–8.1 (br m,1 H, =CH), 11.6–12.6 (br m, 2 H, 2 × NH)
13g (56%)			2.38 (s, 3 H, Me), 2.68 (s, 3 H, Me), 3.77 (s, 3 H, OMe), 6.91 (s, 1 H, Py), 6.99 (d, *J* = 9.0, 2 H, Ar), 7.36 (d, *J* = 9.0, 2 H, Ar), 7.84 (d, *J* = 13.0, 1 H, =CH), 9.07 (s, 1 H, OH), 12.43 (d, *J* = 13.0, 1 H, NH)
12h[e]	$C_{18}H_{15}F_3N_2O_3 \cdot 0.5H_2O$	3100–2640, 1646, 1599, 1576, 1550, 1504	2.10 (s, 3 H, Me), 2.16 (s, 3 H, Me), 5.97–6.03 (br s, 1 H, Py), 7.2–7.5 (m, 5 H, Ph), 8.0–8.2 (br m, 1 H, =CH), 11.6–12.5 (br m, 2 H, 2 × NH)
13h (64%)			2.39 (s, 3 H, Me), 2.69 (s, 3 H, Me), 6.93 (s, 1 H, Py), 7.40–7.45 (m, 5 H, Ph), 7.94 (d, *J* = 12.9, 1 H, =CH), 9.14 (s, 1 H, OH), 12.37 (d, *J* = 12.9, 1 H, NH)

[a] Elemental analyses were within allowed error, C ± 0.36; H ± 0.37; N ± 0.29.
[b] ^1H NMR spectrum recorded in $CDCl_3$.
[c] ^{13}C NMR (DMSO-d_6): δ = 97.98 (q, $^2J_{C,F}$ = 32.6 Hz), 98.98, 116.53, 117.45, 119.98, 122.21, 122.87 (q, $^1J_{C,F}$ = 290.3 Hz), 124.98, 125.67, 129.87, 135.03, 139.18, 147.21, 155.80, 179.81.
[d] ^{19}F NMR (DMSO-d_6): δ = 77.75 (s, CF_3).
[e] A mixture of *Z*- and *E*-isomers.

^1H (400 MHz), ^{13}C (100 MHz) and ^{19}F (376 MHz) NMR spectra were recorded on a Bruker DRX-400 spectrometer in $CDCl_3$ or DMSO-d_6 with TMS and C_6F_6 as internal standards, respectively. The digital resolution for the ^1H NMR spectra was 0.12–0.14 Hz per point. IR spectra were recorded on an Perkin-Elmer Spectrum BX-II instrument as KBr discs. Elemental analyses were performed at the Microanalysis Services of the Institute of Organic Synthesis, Ural Branch, Russian Academy of Sciences. Melting points are uncorrected. All solvents used were dried and distilled per standard procedures. The starting compounds 1 and 5 were prepared by reaction of the appropriate *o*-hydroxyacetyl derivatives with R_FCO_2Et according to described procedures.[20,26] 4-Acetyl-5-hydroxy-3-methyl-1-phenylpyrazole was synthesised by a procedure described elsewhere.[27]

3-(Polyhaloacyl)chromones (2) and their Hetero Analogues (6, 9, 10); General Procedure

A solution of chromanone **1** or **5** or diketone **8** (1.0 mmol) in diethoxymethyl acetate (1.0 g, 6.0 mmol) was heated at 140–150 °C for 15–20 min. After cooling, the resulting mixture was diluted with hexane (3 mL). The solid product obtained on standing was collected by filtration, washed with hexane, and dried to give chromones **2**, **6**, **9** or **10** as colourless crystals (see Table 4).

3-(1-Methoxy-2,2,2-trifluoro-1-hydroxyethyl)-4*H*-chromen-4-one (4a)

A solution of chromone **2d** (250 mg, 1.0 mmol) in MeOH (2 mL) and $CH(OMe)_3$ (1 mL) was saturated with HCl for 10 min at ca. 20 °C. After partial evaporation of the solvent the mixture was left at –10 °C for 2 h. The precipitate of **4a** that formed was filtered and washed with cold MeOH. Without recrystallisation, **4a** was isolated as colourless crystals in analytically pure form; yield: 150 mg (55%); mp 102–103 °C.

IR (KBr): 3345, 3218, 3103, 1639, 1620, 1602, 1574 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 3.44 (s, 3 H, OMe), 7.53 (ddd, ^oJ = 8.1, 7.2 Hz, ^mJ = 1.0 Hz, 1 H, H-6), 7.57 (ddd, ^oJ = 8.6 Hz, ^mJ = 1.0 Hz, ^pJ = 0.5 Hz, 1 H, H-8), 7.81 (ddd, ^oJ = 8.6, 7.2 Hz, ^mJ = 1.7 Hz, 1 H, H-7), 8.25 (s, 1 H, H-2), 8.27 (ddd, ^oJ = 8.1 Hz, ^mJ = 1.7 Hz, ^pJ = 0.5 Hz, 1 H, H-5), 8.94 (s, 1 H, OH).

Anal. Calcd for $C_{12}H_9F_3O_4$: C, 52.57; H, 3.31. Found: C, 52.44; H, 2.96.

3-(1-Ethoxy-2,2,2-trifluoro-1-hydroxyethyl)-4*H*-chromen-4-one (4b)

This compound was synthesised according to the described procedure[19b] in 56% yield as colourless crystals; mp 105–106 °C.

IR (KBr): 3345, 3104, 1640, 1599, 1574 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.28 (t, *J* = 7.1 Hz, 3 H, Me), 3.57 (dq, *J* = 9.6, 7.1 Hz, 1 H, C*H*H), 3.92 (dq, *J* = 9.6, 7.1 Hz, 1 H, CH*H*), 7.52 (ddd, ^oJ = 8.1, 7.2 Hz, ^mJ = 1.0 Hz, 1 H, H-6), 7.56 (br d, 1 H, H-8, ^oJ = 8.6 Hz), 7.80 (ddd, ^oJ = 8.6, 7.2 Hz, ^mJ = 1.7 Hz, 1 H, H-7), 8.26 (dd, ^oJ = 8.1 Hz, ^mJ = 1.7 Hz, 1 H, H-5), 8.27 (s, 1 H, H-2), 8.86 (s, 1 H, OH).

Anal. Calcd for $C_{13}H_{11}F_3O_4 \cdot 0.25H_2O$: C, 53.34; H, 3.96. Found: C, 53.24; H, 3.63.

3-(1-Ethoxy-2,2,3,3-tetrafluoro-1-hydroxypropyl)-7-methoxy-4*H*-chromen-4-one (4c)
This compound was synthesised analogously to **4a** in 66% yield as colourless crystals; mp 97–98 °C.

IR (KBr): 3200, 3093, 1633, 1593, 1567, 1503 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.24 (t, *J* = 7.1 Hz, 3 H, Me), 3.46 (dq, *J* = 9.6, 7.1 Hz, 1 H, C*H*H), 3.87 (dq, *J* = 9.6, 7.1 Hz, 1 H, CH*H*), 3.94 (s, 3 H, OMe), 6.24 (tdd, $^2J_{H,F}$ = 53.3 Hz, $^3J_{H,F}$ = 5.6, 7.4 Hz, 1 H, CF_2CF_2H), 6.91 (d, ^mJ = 2.4 Hz, 1 H, H-8), 7.06 (dd, ^oJ = 9.0 Hz, ^mJ = 2.4 Hz, 1 H, H-6), 8.13 (s, 1 H, H-2), 8.14 (d, ^oJ = 9.0 Hz, 1 H, H-5), 9.18 (s, 1 H, OH).

Anal. Calcd for $C_{15}H_{14}F_4O_5$: C, 51.44; H, 4.03. Found: C, 51.38; H, 3.95.

3-(2,2-Difluoroacetyl)-5,7-dimethyl-4*H*-pyrano[2,3-*b*]pyridin-4-one (6a)
Yield: 77%; mp 151–152 °C.

IR (KBr): 3079, 1720, 1641, 1609, 1537 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.63 (s, 3 H, Me), 2.87 (d, *J* = 0.7 Hz, 3 H, Me), 6.86 (t, $^2J_{H,F}$ = 53.3 Hz, 1 H, CF_2H), 7.15 (s, 1 H, H-6), 8.62 (s, 1 H, H-2).

Anal. Calcd for $C_{12}H_9F_2NO_3$: C, 56.92; H, 3.58; N, 5.53. Found: C, 56.62; H, 3.51; N, 5.57.

7a

^1H NMR ($CDCl_3$, 2%): δ = 2.63 (s, 3 H, Me), 2.85 (d, *J* = 0.7 Hz, 3 H, Me), 6.10 (s, 2 H, 2 × OH), 7.13 (s, 1 H, H-6), 8.35 (s, 1 H, H-2).

5,7-Dimethyl-3-(trifluoroacetyl)-4*H*-pyrano[2,3-*b*]pyridin-4-one (6b) and 5,7-Dimethyl-3-(2,2,2-trifluoro-1,1-dihydroxyethyl)-4*H*-pyrano[2,3-*b*]pyridin-4-one (7b)
Yield: 68%; mp 171–172 °C.

IR (KBr): 3400–3210, 3072, 1732, 1647, 1619, 1604, 1545 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.63 (s, 3 H, Me), 2.87 (d, *J* = 0.7 Hz, 3 H, Me), 7.15 (s, 1 H, H-6), 8.56 (s, 1 H, H-2).

^{19}F NMR ($CDCl_3$): δ = 87.12 (s, CF_3).

Anal. Calcd for $C_{12}H_8F_3NO_3 \cdot 0.25H_2O$: C, 52.28; H, 3.11; N, 5.08. Found: C, 52.26; H, 3.13; N, 4.48.

7b

^1H NMR ($CDCl_3$, 50%): δ = 2.63 (s, 3 H, Me), 2.85 (d, *J* = 0.7 Hz, 3 H, Me), 6.10 (s, 2 H, 2 × OH), 7.13 (s, 1 H, H-6), 8.35 (s, 1 H, H-2).

^{19}F NMR ($CDCl_3$, 55%): δ = 74.93 (s, CF_3).

5,7-Dimethyl-3-(2,2,3,3-tetrafluoropropanoyl)-4*H*-pyrano[2,3-*b*]pyridin-4-one (6c)
Yield: 63%; mp 119–120 °C.

IR (KBr): 3540–3200, 3082, 1713, 1660, 1635, 1611, 1540 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.63 (s, 3 H, Me), 2.86 (d, *J* = 0.7 Hz, 3 H, Me), 6.69 (tt, $^2J_{H,F}$ = 53.2 Hz, $^3J_{H,F}$ = 5.8 Hz, 1 H, CF_2CF_2H), 7.15 (s, 1 H, H-6), 8.48 (s, 1 H, H-2).

Anal. Calcd for $C_{13}H_9F_4NO_3$: C, 51.50; H, 2.99; N, 4.62. Found: C, 51.35; H, 3.04; N, 4.60.

7c

^1H NMR ($CDCl_3$, 13%): δ = 2.63 (s, 3 H, Me), 2.84 (d, *J* = 0.7 Hz, 3 H, Me), 6.23 (s, 2 H, 2 × OH), 6.26 (tt, $^2J_{H,F}$ = 53.2 Hz, $^3J_{H,F}$ = 6.3 Hz, 1 H, CF_2CF_2H), 7.13 (s, 1 H, H-6), 8.33 (s, 1 H, H-2).

1-(5-Hydroxy-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-4,4,4-trifluorobutane-1,3-dione (8b); Typical Procedure
Finely powdered LiH (0.28 g, 35.0 mmol) was added to a solution of ethyl trifluoroacetate (2.0 g, 14.1 mmol) and 4-acetyl-5-hydroxy-3-methyl-1-phenylpyrazole (2.0 g, 9.3 mmol) in anhyd THF (10 mL). The resulting reaction mixture was refluxed for 3 h. Then the solvent was removed by distillation in a water bath under reduced pressure, and a mixture of AcOH (5 mL) and concd HCl (4 mL) was added to the residue. The mixture was refluxed for 5 min and poured onto crushed ice (40 g). The precipitate that formed was filtered off, washed with H_2O, dried, and recrystallised from toluene to give diketone **8b** as yellowish crystals in a yield of 2.7 g (93%); mp 116–117 °C.

IR (KBr): 1655, 1590, 1568, 1501 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.50 (s, 3 H, Me), 6.24 (s, 1 H, =CH), 7.34 (tt, ^oJ = 7.5 Hz, ^mJ = 1.3 Hz, 1 H, H-4′), 7.45–7.50 (m, 2 H, H-3′, H-5′), 7.77–7.81 (m, 2 H, H-2′, H-6′), 11.7 (br s, 1 H, pyrazole-OH), 14.5 (br s, 1 H, enol-OH).

Anal. Calcd for $C_{14}H_{11}F_3N_2O_3$: C, 53.85; H, 3.55; N, 8.97. Found: C, 53.66; H, 3.39; N, 8.74.

1-(5-Hydroxy-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-4,4-difluorobutane-1,3-dione (8a)
This compound was synthesised similarly to **8b** in 87% yield as colourless needle-like crystals; mp 89–90 °C (toluene).

IR (KBr): 1643, 1563, 1495 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.50 (s, 3 H, Me), 6.10 (t, $^2J_{H,F}$ = 54.2 Hz, 1 H, CF_2H), 6.16 (s, 1 H, =CH), 7.33 (tt, ^oJ = 7.5 Hz, ^mJ = 1.3 Hz, 1 H, H-4′), 7.45–7.49 (m, 2 H, H-3′, H-5′), 7.78–7.82 (m, 2 H, H-2′, H-6′), 11.7 (br s, 1 H, pyrazole-OH), 14.4 (br s, 1 H, enol-OH).

Anal. Calcd for $C_{14}H_{12}F_2N_2O_3$: C, 57.15; H, 4.11; N, 9.52. Found: C, 57.37; H, 4.23; N, 9.64.

5-Difluoroacetyl-3-methyl-1-phenylpyrano[2,3-*c*]pyrazol-4(1*H*)-one (9)
Yield: 64%; mp 185–186 °C.

^1H NMR ($CDCl_3$): δ = 2.66 (s, 3 H, Me), 6.91 (t, $^2J_{H,F}$ = 53.3 Hz, 1 H, CF_2H), 7.43 (tt, ^oJ = 7.5 Hz, ^mJ = 1.3 Hz, 1 H, H-4′), 7.52–7.57 (m, 2 H, H-3′, H-5′), 7.73–7.77 (m, 2 H, H-2′, H-6′), 8.35 (s, 1 H, =CH).

^{19}F NMR ($CDCl_3$): δ = 31.03 (d, CF_2H, $^2J_{H,F}$ = 53.3 Hz).

Anal. Calcd for $C_{15}H_{10}F_2N_2O_3$: C, 59.22; H, 3.31; N, 9.21. Found: C, 59.20; H, 3.28; N, 9.23.

Hydrate
^1H NMR ($CDCl_3$, 7%): δ = 2.63 (s, 3 H, Me), 5.57 (s, 2 H, 2 × OH), 5.77 (t, $^2J_{H,F}$ = 56.1 Hz, 1 H, CF_2H), 8.09 (s, 1 H, =CH).

^{19}F NMR ($CDCl_3$, 9%): δ = 28.98 (d, $^2J_{H,F}$ = 56.1 Hz, CF_2H).

3-Methyl-1-phenyl-5-(2,2,2-trifluoro-1,1-dihydroxyethyl)pyrano[2,3-*c*]pyrazol-4(1*H*)-one (10)
Yield: 60%; mp 150–151 °C.

IR (KBr): 3220, 1654, 1597, 1538, 1508 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 2.54 (s, 3 H, Me), 7.46 (t, ^oJ = 7.4 Hz, 1 H, H-4′), 7.57–7.62 (m, 2 H, H-3′, H-5′), 7.80–7.84 (m, 2 H, H-2′, H-6′), 8.25 (br s, 2 H, 2 × OH), 8.48 (s, 1 H, =CH).

Anal. Calcd for $C_{15}H_{11}F_3N_2O_4$: C, 52.95; H, 3.26; N, 8.23. Found: C, 52.61; H, 3.21; N, 7.90.

2-(Alkyl/arylaminomethylene)-2-hydroxy-2-(polyfluoroalkyl)chroman-4-ones (11a–j); General Procedure

A solution of 3-(polyfluoroacyl)chromone **2** (0.4 mmol) and the primary aliphatic or aromatic amine (0.6–0.8 mmol) in MeOH (2–3 mL) was allowed to stand at r.t. for 2 d. The crystalline product that precipitated was filtered off, washed with cold MeOH (1 mL), and dried to give **11** as colourless or yellow crystals (Table 5). Compounds **12a–h** were prepared analogously to **11**, with the exception that the reaction was completed in 1–3 h and was carried out in THF (**12a**, **12c**) or dioxane (**12e–h**).

***trans*-1-(2-Hydroxyphenyl)-3-morpholinoprop-2-en-1-one and Morpholinium Trifluoroacetate**

Yield: 74%; 1:1 mixture; mp 89–90 °C.

^{1}H NMR ($CDCl_3$): δ = 3.17–3.20 (m, 4 H, 2 × CH_2), 3.44–3.47 (m, 4 H, 2 × CH_2), 3.77–3.80 (m, 4 H, 2 × CH_2), 3.93–3.96 (m, 4 H, 2 × CH_2), 5.94 (d, J = 12.4 Hz, 1 H, =CH), 6.82 (ddd, ^oJ = 8.1, 7.2 Hz, ^mJ = 1.2 Hz, 1 H, H-5), 6.95 (dd, ^oJ = 8.4 Hz, ^mJ = 1.2 Hz, 1 H, H-3), 7.37 (ddd, ^oJ = 8.4, 7.2 Hz, ^mJ = 1.6 Hz, 1 H, H-4), 7.66 (dd, ^oJ = 8.1 Hz, ^mJ = 1.6 Hz, 1 H, H-6), 7.83 (d, J = 12.4 Hz, 1 H, =CHN), 9.93 (br s, 2 H, NH_2^+).

Anal. Calcd for $C_{13}H_{15}NO_3{\cdot}C_6H_{10}F_3NO_3$: C, 52.53; H, 5.80; N, 6.45. Found: C, 52.09; H, 5.84; N, 6.30.

(*E*)-3-Anilino-1-(5-hydroxy-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)prop-2-en-1-one (14)

A solution of pyranopyrazole **9** (70 mg, 0.23 mmol) and aniline (43 mg, 0.46 mmol) in MeOH (1 mL) was kept for 24 h at ca. 20 °C. The precipitated crystals were filtered off, washed with MeOH and dried. Compound **14** was obtained as yellow crystals in a yield of 40 mg (55%); mp 156–157 °C. The same compound was obtained from pyranopyrazole **10** after refluxing for 10 min with aniline in *i*-PrOH; yield: 43%.

IR (KBr): 3290, 3208, 3115, 3054, 1671, 1643, 1600, 1591, 1531, 1499 cm^{-1}.

Anal. Calcd for $C_{19}H_{17}N_3O_2{\cdot}0.25H_2O$: C, 70.46; H, 5.45; N, 12.97. Found: C, 70.11; H, 5.23; N, 12.99.

E-Isomer (90%)

^{1}H NMR ($CDCl_3$): δ = 2.44 (s, 3 H, Me), 5.87 (d, J = 12.5 Hz, 1 H, =CH), 7.07–7.22 (m, 5 H, NH, Ar), 7.35–7.44 (m, 4 H, Ar), 7.92–7.96 (m, 2 H, Ar), 8.30 (t, J = 13.0 Hz, 1 H, =CHN).

Z-Isomer (10%)

^{1}H NMR ($CDCl_3$): δ = 2.49 (s, 3 H, Me), 5.53 (d, J = 7.9 Hz, 1 H, =CH), 7.07–7.44 (m, 8 H, Ar), 7.85–7.88 (m, 2 H, Ar), 11.24 (d, J = 13.0 Hz, 1 H, NH).

1-(5-Hydroxy-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-2-(4-nitroanilinomethylene)-4,4,4-trifluorobutane-1,3-dione (15)

A solution of pyranopyrazole **10** (100 mg, 0.29 mmol) and *p*-nitroaniline (60 mg, 0.44 mmol) in *i*-PrOH (3 mL) was refluxed for 10 min. Then the solvent was evaporated, and the residue was recrystallised from MeOH. Compound **15** was obtained as yellow crystals in a yield of 100 mg (72%); mp 157–158 °C.

IR (KBr): 3200–3080, 1644, 1599, 1555, 1534, 1504, 1490 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 2.44 (s, 3 H, Me), 3.58 (br s, 2 H, H_2O), 7.41 (t, ^oJ = 7.4 Hz, 1 H, H-4′), 7.55–7.60 (m, 2 H, H-3′, H-5′), 7.61–7.73 (m, 4 H, C_6H_4), 7.95 (d, J = 12.3 Hz, 1 H, =CH), 8.22–8.26 (m, 2 H, H-2′, H-6′), 10.25 (br s, 1 H, OH), 12.14 (br d, J = 12.0 Hz, 1 H, NH).

Anal. Calcd for $C_{21}H_{15}F_3N_4O_5{\cdot}H_2O$: C, 52.73; H, 3.58; N, 11.71. Found: C, 52.76; H, 3.60; N, 11.48.

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