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Reactions of 3-(polyfluoroacyl)chromones with hydroxylamine: synthesis of novel R^F-containing isoxazole and chromone derivatives

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ABSTRACT

Reaction of 3-(polyfluoroacyl)chromones with hydroxylamine free base proceeds via nucleophilic 1,4-addition followed by opening of the pyrone ring and subsequent cyclization to 4-(polyfluoroalkyl)-4*H*-chromeno[3,4-*d*]isoxazol-4-ols in good yields. On treatment with trifluoroacetic acid, the isoxazole ring of this annulated heterocyclic system opens to give 3-cyano-2-(polyfluoroalkyl)chromones, which were successfully hydrolyzed with concentrated H_2SO_4 to afford 3-carbamoyl-2-(polyfluoroalkyl)chromones. On the other hand, oximation of 3-(polyfluoroacyl)chromones with hydroxylamine hydrochloride occurs either at the carbonyl carbon atom connected to the R^F group or at the C-2 atom to give 3-R^FC(=NOH)-chromones and 5-R^F-4-salicyloylisoxazole oximes, respectively. The former were easily converted to 3-R^F-4-salicyloylisoxazoles by simple heating in dimethyl sulfoxide.

1. Introduction

3-Formyl- and 3-acylchromones **1** have attracted attention long ago as highly reactive compounds, which can serve as the starting substances in the syntheses of a whole series of heterocycles with useful properties due to three strong electrophilic centers (C-2 and C-4 atoms of the chromone system and the carbonyl carbon of 3-RCO group).[1] In the chromone ring, the oxygen atom at the 1-position diminishes electron density on the adjacent C-2 atom and two carbonyl groups withdraw electrons through a double bond, hence the 2-position of 3-acylchromones **1** is highly reactive toward the nucleophiles. That is why the reactions of these compounds with such dinucleophiles as hydroxylamine and hydrazines start predominantly from the attack of the unsubstituted C-2 atom (1,4-addition) and are accompanied by pyrone ring-opening to form the β-dicarbonyl intermediate capable of regioselective intramolecular heterocyclizations.[1] Along with this route, the initial attack can occur at the 3-RCO group as well (1,2-addition), which does not exclude the variant of recyclization due to the intramolecular Michael addition and the subsequent ring-opening reaction.[2] Thus, the reactions of 3-formylchromone **1a**,[3] 3-benzoylchromone **1b**,[4] and 3-acetylchromone **1c**[5] with hydroxylamine have been shown to give chromone derivatives **2a**,**b** and **3a**–**c** and regioisomeric isoxazoles **4a**–**c** and **5a**,**b**, depending on the reaction conditions. These products can result from the initial nucleophilic 1,2- or 1,4-additions of hydroxylamine to **1a** (due to chemical equivalency of the 3-CHO group and C-2 atom) and 1,4-addition to **1b**,**c**. In the latter case, no 1,2-addition of hydroxylamine to the PhC=O and MeC=O double bonds was observed (Fig. 1).

Trifluoromethylated heterocycles continue to be of great academic and industrial interest, because the replacement of hydrogen by the fluorine atom sometimes brings about a dramatic change in the physical properties, chemical reactivity, and biological activity of the derived fluorinated compounds arising as a result of the high electronegativity of fluorine and high C–F bond energy.[6] However, in contrast to well studied 3-formylchromones **1a**[7] and 3-acylchromones **1b**,**c**[8] no data on the reaction of 3-(polyfluoroacyl)chromones **6**[9] with hydroxylamine have been documented. In connection with this, and as an extension of our studies on the synthetic potential of 3-(polyfluoroacyl)chromones **6**, which turned out to be highly reactive substrates in the reactions with mono- and dinucleophiles,[10] we decided to investigate their reactions with hydroxylamine under basic and acidic conditions in order to develop a simple synthesis of novel R^F-containing isoxazole and chromone derivatives (preliminary communication[11]).

One would expect that the reactions of chromones **6** with 1,2-nucleophilic reagents, such as hydrazine and hydroxylamine,

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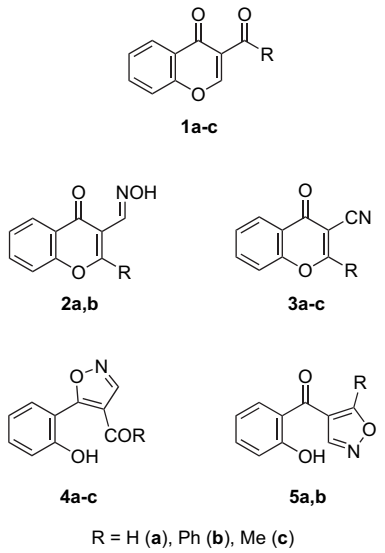
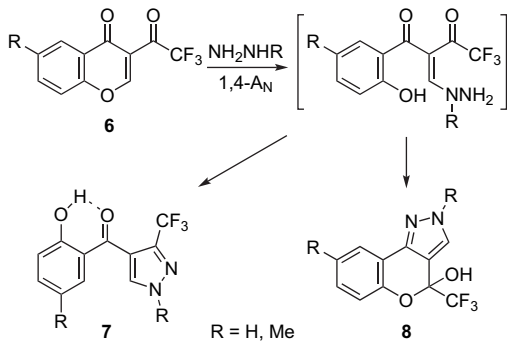


Figure 1. Products from the reaction of 3-acylchromones with hydroxylamine.

would lead to the possibility of competition between different initial nucleophilic attacks and then toward different cyclization patterns. In fact, we have recently shown[12] that the main direction of the reaction of 3-(trifluoroacetyl)chromones **6** with hydrazine hydrate and methylhydrazine is the 1,4-addition followed by opening of the pyrone ring and subsequent ring closure to the CF_3CO group (pyrazoles **7**) or to the carbonyl at the aromatic ring (pyrazoles **8**) (Scheme 1).



Scheme 1.

In the present paper, we wish to report that treatment of chromones **6** with hydroxylamine leads to five types of products, depending on the reaction conditions and the nature of the substituents.

2. Results and discussion

2.1. 4-R^F-Chromeno[3,4-*d*]isoxazol-4-ols and 5-R^F-4-salicyloylisoxazoles

We found that 3-R^FCO-chromones **6a**–**h** smoothly reacted with hydroxylamine to afford chromeno[3,4-*d*]isoxazoles **9a**–**h** in moderate to good yields (except for 3-CCl_3CO-chromone **6h**). All the reactions were carried out in methanol at room temperature using hydroxylamine (2 equiv) obtained in situ from the corresponding hydrochloride after reaction with potassium hydroxide (method A). Furthermore, the same products were obtained in lower yields when chromones **6** were treated with a combination of $NH_2OH\cdot HCl$ and AcONa in methanol (method B). Compounds **9** represent a cyclic form of 5-(2′-hydroxyaryl)-4-(polyfluoroacyl)isoxazoles, which appears due to the addition of phenolic OH to the carbonyl group of the polyfluoroacyl substituent. It is noteworthy that the structure of isoxazoles **9** indicates unambiguously the initial attack of hydroxylamine at the electrophilic C-2 atom (1,4-addition) followed by ring-opening to intermediate **A**, which then undergoes heterocyclization to the carbonyl at the benzene ring (only in this case the R^FCO group remains free and can participate in the formation of cyclic semiketal form **9**).

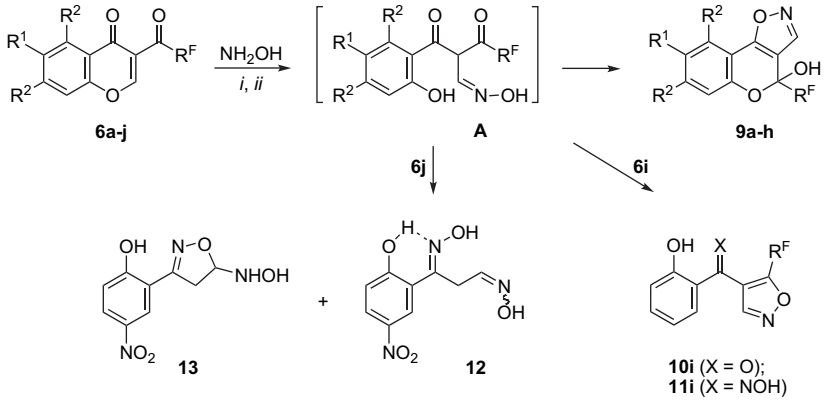
The alternative cyclization of **A** involving the oxime hydroxyl and the carbonyl carbon connected to the R^F group to give 5-R^F-isoxazoles **10** occurs only in the case of 3-CF_2HCO-chromone **6i**. When **6i** was employed, a 10:1 mixture of 5-CF_2H-4-salicyloylisoxazole **10i** and its oxime **11i** was obtained with hydroxylamine free base (method A). Recrystallization of this mixture from toluene–hexane (1:3) afforded a pure sample of the major product **10i**. The same result was achieved in the presence of AcONa (method B) with the only difference that the selectivity of the reaction decreases and the ratio of compounds **10i** and **11i** becomes equal to 4:1, respectively. Thus, in the basic and weakly acidic conditions compounds **9a**–**h** and **10i** are formed, most probably, through common intermediate **A** (Scheme 2), which, in the case of starting chromones **6a**–**h**, undergoes ring closure to the carbonyl carbon atom at the aromatic ring, whereas for **6i** the ring closure proceeds at the carbonyl connected to the CF_2H group. The firmest distinction between the isomeric 5-CF_2H-isoxazole **10i** and 3-CF_2H-isoxazole **15i** (see below, Scheme 3) was obtained from the mass spectrum fragments arising from loss of the CF_2H group at the 5-position of the isoxazole ring (m/z 188 $[M-CF_2H]^+$ (92)).[13]

Noticeably, the nature of the substituents on the benzene ring do not have any major effect on the reaction outcome. At the same time, 6-nitrochromones **6g**,**j**, readily available from the nitration of chromones **6c**,**a**, respectively, with 96% HNO_3 and H_2SO_4 at 75 °C for 1.5 h, reacted with hydroxylamine to give different products, depending on the length of the polyfluoroalkyl group. Thus, if the reaction of hydroxylamine is carried out with **6g** ($R^F=(CF_2)_2H$), compound **9g** was isolated in 24% (method A) and 51% (method B) yields, whereas chromone **6h** ($R^F=CF_3$) reacted with hydroxylamine under the same reaction conditions affording a mixture of two geometrical isomers of dioxime **12** (*syn*/*anti* isomers) and isoxazoline **13** (ring-chain isomer) in the ratio of **12**/**13**=(55+40):5 and in 40% yield, as it was observed earlier in the reaction of the unsubstituted chromone with hydroxylamine.[14] In our case, the CF_3CO group seems to behave like a good leaving group and detrifluoroacetylation took place as an unwanted reaction (Scheme 2).

The structures of **9a**–**h** were confirmed with the help of spectral and analytical data. A characteristic feature of the ^1H NMR spectra of compounds **9** in $CDCl_3$ is the appearance of a broadened singlet at δ 3.9–4.7 ppm for the OH group and a signal at δ 8.4–8.5 ppm for the H-3 proton as a quartet or triplet with $^5J_{H,F}$=0.6–1.1 Hz; in DMSO-d_6 these protons appeared as singlets at δ 9.2–9.5 and 8.9–9.0 ppm, respectively. In the cases of compounds **9c**,**d**,**g**, the attachment of the $(CF_2)_2H$ group to a chiral center is clearly supported by the ^1H NMR spectra, in which the terminal hydrogen atom of this group (δ 6.20–6.22 ppm) is split into a triplet of doublets of doublets with $^2J_{H,F}$=52.5–52.7 Hz and $^3J_{H,F}$=7.3–7.7, 4.1–4.3 Hz instead of the usual triplet of triplets. In the ^{19}F NMR spectra the CF_3 group of **9a**,**f** manifests itself as a singlet or doublet with $^5J_{F,H}$=0.9 Hz at ~76.5 ppm (C_6F_6); the ^{13}C NMR spectrum of **9a** exhibits a quartet ($^1J_{C,F}$=285.7 Hz) at 121.4 ppm for the carbon of the CF_3 group and a quartet ($^2J_{C,F}$=36.3 Hz) at 95.6 ppm for the *C*–CF_3. This confirms that the CF_3 group is bonded to the sp^3 hybridized carbon atom.

2.2. Chromone 3-R^F-oximes, 3-R^F-4-salicyloylisoxazoles, and 5-R^F-4-salicyloylisoxazole oximes

We found that chromones **6b**,**c**,**i**,**k** react in different manner with hydroxylamine hydrochloride in refluxing methanol or



Reaction conditions (*i*): $NH_2OH \cdot HCl$, KOH, MeOH, rt (method A);
(*ii*): $NH_2OH \cdot HCl$, AcONa, MeOH, rt (method B)

Chromone	R^F	R^1	R^2	Product	Yield[a] (%)
6a	CF_3	H	H	**9a**	72[b], 48[c]
6b	CF_3	Me	H	**9b**	65[b], 44[c]
6c	$(CF_2)_2H$	H	H	**9c**	70[b]
6d	$(CF_2)_2H$	Me	H	**9d**	57[b]
6e	$(CF_2)_2H$	H	Me	**9e**[d]	40[b,c]
6f	CF_3	Cl	H	**9f**	54[b]
6g	$(CF_2)_2H$	NO_2	H	**9g**	24[b], 51[c]
6h	CCl_3	H	H	**9h**	10[b]
6i	CF_2H	H	H	**10i**[e]	55[b], 20[c]
6j	CF_3	NO_2	H	**12**[f]	40[b]

[a] Isolated yields.
[b] Method A.
[c] Method B.
[d] A 3:1 mixture of **9e** and **16e**.
[e] A mixture of **10i** and **11i**.
[f] A mixture of **12** and **13**.

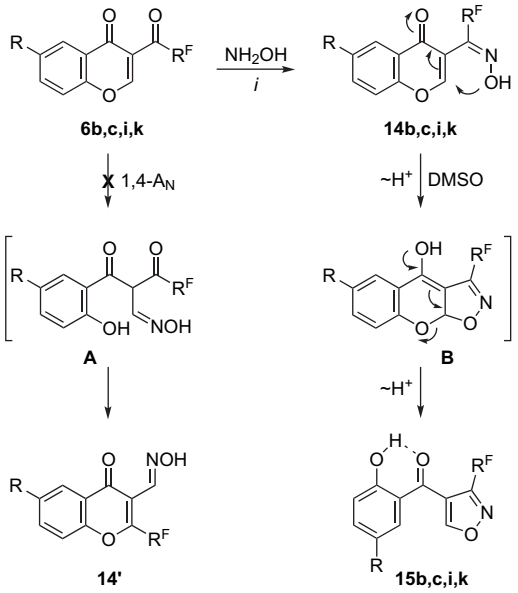
Scheme 2.

ethanol in the presence of a catalytic amount of concentrated HCl for 5 h (method C).[2,3a] Under strongly acidic conditions the only products isolated were the corresponding chromone 3-R^F-oximes **14b**,**c**,**i**,**k**, formed undoubtedly by nucleophilic 1,2-addition of hydroxylamine to the R^FCO group (Scheme 3). This result is in marked contrast to those obtained by Eiden et al.[4] and Ghosh et al.,[5] in which they found that the addition of hydroxylamine to 3-benzoylchromone **1b** and 3-acetylchromone **1c** occurred exclusively at the 2-position (Fig. 1, compounds **2b**–**5b**, **3c**, **4c**). Oximes **14** were obtained in 24–45% yields and no starting material was recovered, which may suggest that decomposition of the starting chromones **6** under the reaction conditions accounts for the incomplete mass balance. A similar reaction with chromone **6a** gave no isolated products. All the compounds **14** were identified with ^1H, ^{19}F, ^{13}C NMR and IR spectroscopies, and by elemental analyses.

The structure of chromone oxime **14c** was established by consideration of the $^3J_{H,F}$ value of 5.3 Hz for the terminal proton of the $(CF_2)_2H$ group. This value agrees well with the data for compounds with a $(CF_2)_2H$ group at the oxime carbon atom ($^3J_{H,F}$=5.4 Hz in the case of oximes[15] and $^3J_{H,F}$=3.0–3.8 Hz in the case of 2-(1,1,2,2-tetrafluoroethyl)chromones[16]). This allowed us to reject the alternative structure **14′**, which can result from the initial nucleophilic 1,4-addition via intermediate **A** (Scheme 3). The *E*-configuration of the C=N bond was suggested from the ^{19}F NMR chemical shift of the CF_3 group in oxime **14b** (93.4 ppm, C_6F_6). According to published data,[17] the signal for this group in the spectra of *Z*-isomers of trifluoromethylated oximes and hydrazones appeared at 97–99 ppm, whereas for the *E*-isomers it appeared at 92–96 ppm.

In addition, all signals in the ^1H and ^{13}C NMR spectra of compound **14i** were assigned on the basis of 2D HSQC and HMBC experiments. Since the C-2 atom is not bonded to the CF_2H group and the HMBC spectrum displayed cross-peaks between the resonances of the H-2 and the carbon atoms C-3, C-4, C-8a, and C=N, the structure **14′** is excluded. Thus, the regiochemistry was determined and higher reactivity of a R^FCO group than C-2 atom of **6** toward the amino group of hydroxylamine in acidic conditions was shown. The ^1H NMR spectra of chromone oximes **14** in $CDCl_3$ displayed the expected singlets at δ 7.96–8.10 and 8.61–8.85 ppm (δ 8.47–8.50 and 12.44–12.86 ppm in DMSO-d_6) due to H-2 and OH, respectively. The IR spectra of **14** recorded in KBr showed three distinct absorption bands at 1620–1630, 1650–1665, and 3200–3250 cm^{-1} assigned to the C=N, C=O, and OH functions, respectively.

The initial attack of the R^FCO group does not exclude the recyclization of chromone 3-*E*-oximes **14** to the isomeric 3-R^F-isoxazoles **15** due to the intramolecular Michael addition (Scheme 3, intermediate **B**) and the subsequent ring-opening reaction.[2] In this case, a rearrangement between **14** and **15** may be involved. Oximes **14** were thermally stable enough to be recrystallized from a toluene–hexane (1:1) mixture, however, the rearrangement was markedly favored when carried out in DMSO as a solvent even at room temperature. Indeed, we found that oximes **14** on dissolution in DMSO-d_6 spontaneously rearrange into 3-(polyfluoroalkyl)-4-



Reaction conditions (*i*): NH_2OH•HCl, MeOH, reflux (method C)

Chromone	R^F	R	Oxime	Yield (%)
6b	CF_3	Me	**14b**	28
6c	$(CF_2)_2H$	H	**14c**	24
6i	CF_2H	H	**14i**	45
6k	CF_2H	Cl	**14k**	35

Scheme 3.

salicyloylisoxazoles **15** and monitored the reaction progress by ^1H NMR (Table 1). The application of 2D HSQC and HMBC NMR techniques has made it possible to assign all the signals in the mixture. At 24 °C after only 1 min the spectrum of **14i** already showed the presence of resonances at 10.65 (phenolic OH) and 9.71 ppm (isoxazolic H-5), while in 3 h isoxazole **15i** was the predominant species in a mixture with starting material. A similar transformation with different reaction rates was observed in all the chromone oximes **14**. The sensitivity of the reaction rate to electronic effects can be seen in the behavior of 6-chlorochromone oxime **14k**. It should be emphasized that in $CDCl_3$ only one set of signals attributed to **14** was observed. The rearrangement of **14** occurs on storing at room temperature for some months and could be easily achieved also by heating above their melting point. Note that mass spectra of **14b** and **15b** are identical.

In a pure form 3-R^F-isoxazoles **15** were isolated in 62–70% yields after heating of **14** in DMSO-d_6 at 85 °C for 5 h (the reaction conditions were not optimized). To the best of our knowledge, 3-formylchromone 3-oximes have not been examined in a ring-to-ring rearrangement, although the reaction of 3-formylchromones with hydroxylamine without isolation of the intermediate 3-oximes was used for the preparation of 4-salicyloylisoxazoles **5a**.[2] The driving force for the irreversible interconversion **14**→**15** is thermodynamic

Table 1
Heterocyclic rearrangement of **14i**,**k** to **15i**,**k** in DMSO-d_6 at 24 °C

Reaction time	Ratio of **14i**/**15i**	Reaction time	Ratio of **14k**/**15k**
1 min	90:10	1 min	62:38
45 min	70:30	2.5 h	8:92
1.5 h	65:35	6.5 h	2:98
3 h	45:55	27 h	0:100
20 h	25:75		
50 h	18:82		

10i

121.2 (t, C-4, $^3J_{C,F}$ = 4.6 Hz),
151.4 (C-3),
162.6 (t, C-5, $^2J_{C,F}$ = 25.4 Hz)

15i

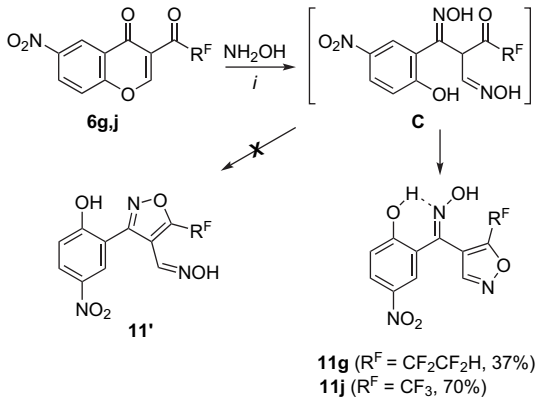
119.0 (t, C-4, $^3J_{C,F}$ = 1.7 Hz),
156.0 (t, C-3, $^2J_{C,F}$ = 24.9 Hz),
166.3 (C-5)

Figure 2. ^{13}C NMR data for regioisomeric isoxazoles **10i** and **15i**.

in nature[18] and the higher stability of the formed isoxazole ring, with respect to the starting chromone 3-oxime, plays an important role. This reaction is consistent with the *E*-configuration of the oxime C=N bond, which was deduced on the basis of the ^{19}F NMR chemical shift of the CF_3 group.

The structures of isoxazoles **15** were confirmed by their elemental and spectral analyses, including 2D HSQC and HMBC experiments for **15i**. Regioisomeric isoxazoles **15i** and **10i** could be easily distinguished by their ^1H and ^{13}C NMR spectra (Fig. 2). The diagnostic triplet for the isoxazole proton in 3-CF_2H-isoxazole **15i**, which appeared at 9.71 ppm with $^5J_{H,F}$=1.5 Hz, was shifted upfield in 5-CF_2H-isoxazole **10i** (triplet at 9.08 with $^5J_{H,F}$=1.7 Hz), that is, in **15i** this proton is more deshielded than in **10i** due to the neighboring oxygen atom of the isoxazole ring.

In contrast to **6b**,**c**,**i**,**k**, refluxing chromones **6g**,**j** bearing the electron-withdrawing nitro group with hydroxylamine hydrochloride in methanol for 5 h (method C) led to the formation of 5-R^F-4-salicyloylisoxazole oximes **11g**,**j**. Only one regioisomer has been obtained in this reaction in 37 and 70% yields, respectively. The mass spectrum of **11j** exhibited a molecular ion at *m*/*z* 317 $[M]^+$ (83), consistent with the addition of two hydroxylamine molecules to **6j**, and the most intense signal at *m*/*z* 248 $[M-CF_3]^+$ (100) indicating that the major fragmentation pathway involves cleavage of a trifluoromethyl group. Hence, these compounds belong to the series of 5-CF_3-isoxazoles and the reaction proceeds via the mechanism of nucleophilic 1,4-addition followed by pyrone ring-opening with concomitant addition of a second molecule of NH_2OH (intermediate **C**) and subsequent ring closure involving the oxime hydroxyl and R^FCO group. This fact seems to indicate that the pyrone ring-opening is facilitated by the presence of an electron-withdrawing substituent in the *para* position of the heterocyclic oxygen (Scheme 4). Non-fluorinated oxime of 4-salicyloylisoxazole was obtained by Basiński et al. from the reaction of chromone 3-oxime **2a** with hydroxylamine hydrochloride in ethanol.[3f,g]



Reaction conditions (*i*): NH_2OH•HCl, MeOH, reflux (method C)

Scheme 4.

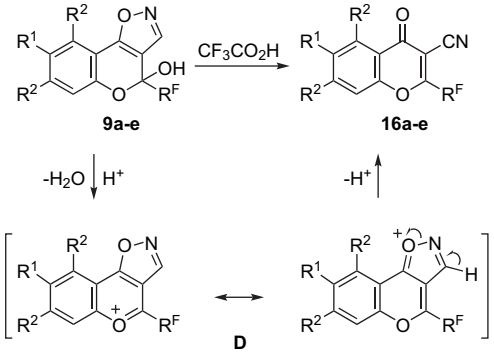
The choice between the isomeric 5-R^F-isoxazoles **11** and **11′** (the latter arises from initial attack at the R^FCO carbonyl by the hydroxyimino group connected to the aromatic ring) was made in favor of the former on the basis of analysis of 2D HSQC and HMBC spectra. In a DMSO-d_6 solution of compound **11j**, the phenolic and oximic protons appear as narrow singlets (δ_{OH}=11.56 ppm and δ_{NOH}=12.58 ppm) due to the absence of an exchange process that allows to observe cross-peaks between these protons and carbon atoms. In particular, the HMBC spectrum exhibits the cross-peaks between the proton of the NOH group and non-protonated C=N carbon at 141.3 ppm, as well as between the aromatic proton H-6′ and carbon of C=N. Hence, structure **11′** bearing CH=NOH moiety is excluded. In addition, the isoxazole proton H-3 is bound due to the $^2J_{C,H}$ and $^3J_{C,H}$ coupling constants with the carbon atoms C-4 and C-5, but none with the oxime carbon atom. Similar correlations were also observed for 3-CF_2H-isoxazole **15i**. These results show that the framework of molecules **11** and **15** consists of two nonplanar to each other parts: the isoxazole cycle and the benzene ring with oxime or keto groups lying in the same plane. Apparently, the intramolecular O–H···N=C and O–H···O=C hydrogen bonds are responsible for the planar structure of the second fragment.

Thus, we demonstrated a subtle influence of the remote substituent on the reactivity of 3-R^FCO-chromones **6** with hydroxylamine hydrochloride. The change in the reaction pathway in the case of **6g,j** is probably due to the fact that the attack on the C-2 atom is accompanied by the cleavage of the C–O bond, and the strong electron-withdrawing NO_2 group favors stabilization of the leaving phenolate anion, thus facilitating the pyrone ring-opening. It is interesting that chromone **6g** reacted with hydroxylamine via only 1,4-addition to afford isoxazoles **9g** or **11g** depending on the reaction conditions. By proper choice of the pH of the medium these compounds could be selectively obtained in 37–51% yields. On the whole, the above results show that acidic conditions facilitate the addition reaction at the R^FCO group. This observation is not completely unexpected, considering that the R^F group complicates a dehydration stage due to the destabilization of the intermediate carbocation and, therefore, the formation of the aromatic isoxazole ring and chromone 3-oxime is hindered under the basic reaction conditions.

2.3. 3-Cyano-2-R^F-chromones

3-Cyanochromones are important intermediates in the synthesis of biologically interesting compounds.[19] On the other hand, due to the powerful electron-withdrawing ability of R^F groups, the insertion of polyfluoroalkyl substituents into the 2-position of chromones activates these molecules and 2-R^F-chromones are highly reactive substrates in reactions with various *N*-, *S*-, and *C*-nucleophiles.[20] Although a number of synthetic methods for the preparation of 3-cyanochromones,[19] including 3-cyano-2-methylchromones[5,21] and 3-cyanoflavone,[4] have been reported, only one patent on the synthesis of 3-cyano-7-hydroxy-2-(trifluoromethyl)chromone from 2,4-dihydroxybenzoyl acetonitrile and trifluoroacetic anhydride have appeared in the literature,[19i] despite the possible enhancement of their reactivity due to the presence of the CF_3 group. In connection with this, we examined the possibility of preparing 3-cyano-2-(polyfluoroalkyl)chromones **16** from compounds **9**.

Attempts to obtain 3-cyano-2-R^F-chromones **16** from chromeno[3,4-*d*]isoxazoles **9** in the presence of KOH in ethanol, conditions that had previously been used for the preparation of 3-cyanoflavone **3b** from **2b**, **4b**, and **5b**,[4] proved fruitless. However, it was found that the required compounds **16** could be easily prepared by refluxing isoxazoles **9** in trifluoroacetic acid for 15 min (only starting material was recovered from a similar reaction in acetic acid). Thus, isoxazoles **9a–d** are easily ring opened to give 3-cyano-2-(polyfluoroalkyl)chromones **16a–d** in high yields. This result probably represents a specific property of fused isoxazoles **9** because only base-induced ring-opening reactions have been reported for non-fluorinated analogues **4** and **5**.[2,3a,4] A possible mechanism for the trifluoroacetic acid ring-opening of **9** is outlined in Scheme 5. We favor the pathway involving the intermediacy of the aromatic benzopyrylium cation **D** since its formation via elimination of water is especially facile under acidic conditions. Subsequent deprotonation of cation **D** with concomitant isoxazole ring-opening leads to 3-cyano-2-R^F-chromones **16**. However, we cannot exclude the formation of the intermediate chromone 3-oxime **14′** (Scheme 3), which is readily dehydrated to **16** under these conditions. The simple and efficient synthesis of 3-cyano-2-R^F-chromones **16** is of doubtless interest, because this class of organic compounds remained inaccessible and unstudied up to now.

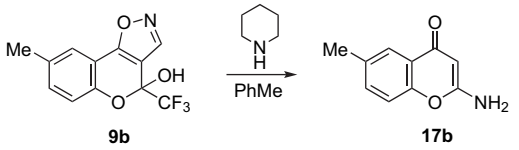


Nitrile	R^F	R^1	R^2	Yield (%)
16a	CF_3	H	H	83
16b	CF_3	Me	H	72
16c	$(CF_2)_2H$	H	H	85
16d	$(CF_2)_2H$	Me	H	71
16e	$(CF_2)_2H$	H	Me	73

Scheme 5.

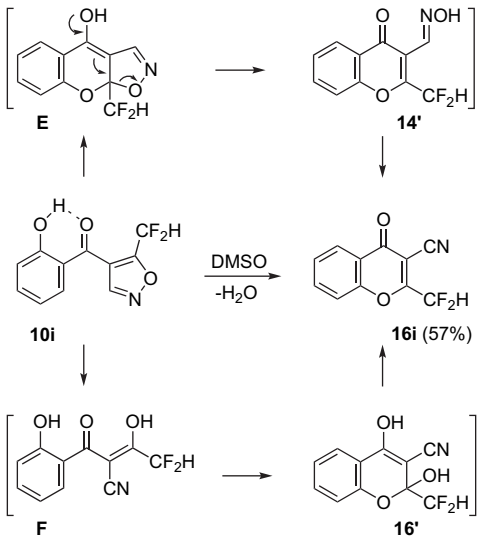
Surprisingly, isoxazoles **9f,g** failed to provide the corresponding carbonitriles **16f,g** and only starting materials were recovered under the same reaction conditions. In the case of **9f**, besides the starting material, 5-(5-chloro-2-hydroxyphenyl)isoxazole (18%), which is likely the result of the detrifluoroacetylation of **9f**, and unidentified product (12%) were detected by ^1H NMR spectroscopy. On the other hand, chromone **6e** bearing two electron-donating methyl groups reacted with hydroxylamine (methods A and B) to afford a 3:1 mixture of **9e** and **16e**, which was converted to carbonitrile **16e** by simple crystallization from toluene (**9e** was converted to **16e** during crystallization). All our attempts to obtain **9e** as the sole product were fruitless. Thus, it appears that electronic effects play an important role in the ring-opening of isoxazoles **9** to carbonitriles **16** (the presence of the electron-withdrawing substituents, such as Cl and NO_2, on the benzene ring inhibit and the electron-donating methyl group facilitates this process). This observation is consistent with our assumption that the reaction proceeds via the intermediate benzopyrylium cation **D**, the destabilization of which by electron-withdrawing substituents would increase the energy barrier to dehydration. As a result, **9f,g** are sufficiently stable in CF_3CO_2H solution. Isoxazole **9b** was unchanged in acetic acid and ethanolic KOH at heating for 15 min, however, when a solution of **9b** in toluene in the presence of piperidine was refluxed for 10 min, the loss of the trifluoroacetyl group took place cleanly to lead to the formation of 2-amino-6-methylchromone **17b** in 62% yield (Scheme 6). Note that the loss of

CF_3CO moiety in some reactions of trifluoromethyl β-dicarbonyl compounds is a known phenomenon.[10c,22a]



Scheme 6.

It is commonly known[22b] that isoxazoles having a free 3-position are less stable toward bases than those having a substituent in the 3-position. We found that on reflux in DMSO for 5 min, isoxazole **10i** undergoes the ring-opening/ring-closure sequence to form 3-cyano-2-(difluoromethyl)chromone **16i** in 57% yield. According to the ^{1}H NMR spectroscopic data, this irreversible process is evident immediately on simple dissolution of **10i** in DMSO-d_6 (9% of **16i** after 1–2 min) and there is subsequent change in the percentage rearrangement (18% of **16i** after 2.5 h). In $CDCl_3$, reaction does not occur, only the starting material **10i** being present. It is obvious that 5-CF_2H-isoxazole **10i** is initially formed as the kinetically controlled product, which in DMSO-d_6 easily undergoes rearrangement via an intramolecular attack of phenolic hydroxyl on the electrophilic C-5 atom of the isoxazole ring (intermediate **E**) with concomitant opening of the isoxazole ring and subsequent dehydration of intermediate aldoxime **14′** (non-isolable) to the thermodynamically controlled chromone product **16i**. Also, we cannot exclude the alternative deprotonation of the isoxazole ring followed by ring-opening with cleavage of the N–O bond (intermediate **F**) and dehydration of **16′** (non-isolable) to **16i** (Scheme 7).



Scheme 7.

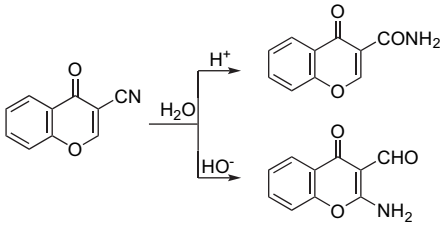
Similar transformation in the series of non-fluorinated 4-salicyloylisoxazoles has been described previously,[2,3a] however, 3-cyanochromones were obtained in very low yields (2–3%).[2] Apparently, the strong electron-withdrawing nature of the CF_2H group plays an important role in the acceleration of this reaction. Thus, contrary to 3-R^F-isoxazoles **15**, isoxazoles **9** and **10** with the 3-position vacant can be considered as aldoximes in protected form, having a masked cyano group. However, (2′-hydroxy-5′-nitrophenyl)[5-(trifluoromethyl)isoxazol-4-yl]methanone oxime **11j** failed to produce the chromone ring under the same reaction conditions.

The ^{1}H, ^{19}F, and ^{13}C NMR spectra of chromones **16** displayed the expected signals. In the ^{1}H NMR spectra the most diagnostic parameter for structural assignment is the chemical shift for the H-5 proton, which was shifted downfield to δ 8.05–8.28 ppm due to the deshielding effect of the carbonyl group in the *peri*-position as indicated in the case of chromones.[23] The IR spectra of **16** in KBr showed two intense peaks at 1662–1680 and 1627–1639 cm^{-1}, which are ascribed to C=O and C=C absorptions, respectively. The weak CN absorptions observed at 2237–2245 cm^{-1} are typical for CN systems substituted by strong electron-withdrawing groups.[24]

2.4. Some reactions of 3-cyano-2-R^F-chromones

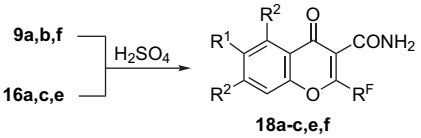
The high reactivity of 2-R^F-chromones and their application as key intermediates in various transformations for the preparation of fluorine-containing compounds[20] provided the motivation for further studies dealing with the reactivity of 3-cyano-2-R^F-chromones. We anticipated that these compounds, as a result of the presence of the CN group, might undergo nucleophilic addition reactions and intramolecular heterocyclizations giving various heterocycles bearing an R^F group more easily than the previously studied 2-R^F-chromones.[20]

Among the diverse transformations of 3-cyanochromones, one of the more interesting reactions that has been encountered is the conversion of these compounds, on heating with morpholine in aqueous DMF[19b] or in the presence of NaOH in water,[3d] to 2-amino-3-formylchromones in high yields. Thus, 3-cyanochromone is 'chemically equivalent' to 2-amino-3-formylchromone under certain reaction conditions.[19g] On the other hand, under strongly acidic conditions this carbonitrile hydrolyzes to chromone-3-carboxamide.[3c,19c,h] (Scheme 8).



Scheme 8.

When 3-cyano-2-R^F-chromones **16** were treated with concentrated H_2SO_4 at 90 °C for 3 h, 3-carbamoyl-2-R^F-chromones **18** were obtained in high yields. It was also found that the carbonitrile precursors, chromeno[3,4-*d*]isoxazoles **9**, could be employed directly in this reaction to effect a more practical synthesis of **18** (Scheme 9). Previously, 7-hydroxy-2-(trifluoromethyl)chromone-3-carboxamide was obtained by the reaction of 7-hydroxy-2-(trifluoromethyl)chromone-3-carbonitrile with sulfuric acid at 120–135 °C for 1.5 h.[19i]



18a-c,e,f

Amide	R^F	R^1	R^2	Yield (%)
18a	CF_3	H	H	80[a], 74[b]
18b	CF_3	Me	H	75
18c	$(CF_2)_2$H	H	H	75
18e	$(CF_2)_2$H	H	Me	68
18f	CF_3	Cl	H	77

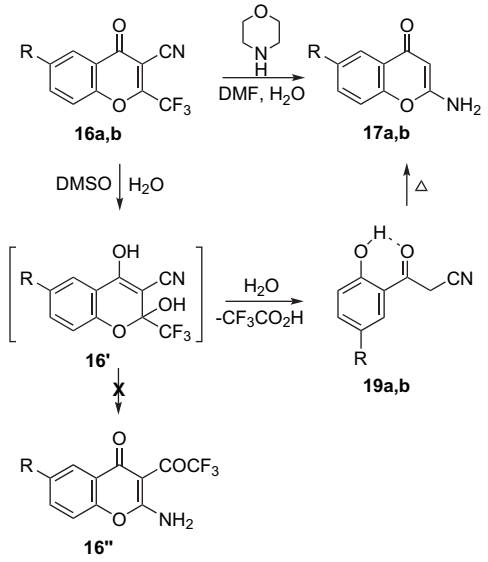
[a] From **9a**.
[b] From **16a**.

Scheme 9.

In the ^{1}H NMR spectra of **18** the signal of the H-5 proton appeared at δ 7.90–8.12 ppm and two broadened singlets of the NH_2 group appeared at δ 7.74–7.93 ppm. The IR spectra of **18** exhibited two or three intense absorption bands at 3190–3410 cm^{-1} due to the amino group and three intense bands at 1608–1695 cm^{-1}, corresponding to the double bond, the chromone, and amide carbonyl groups.

All our attempts to prepare 2-R^F-chromone-3-carboxylic acids from **16** and **18** were fruitless. For instance, attempts to hydrolyze **16a**,**b** with 55% sulfuric acid at 130 °C or with concentrated HCl at reflux for 2 h, conditions that had previously been used for the hydrolysis of 3-cyanochromone to chromone-3-carboxylic acid,[3c,19c,h] only caused the recovery of unchanged starting materials. It should be noted that 2-(trifluoromethyl)chromone-3-carboxylic acid ethyl ester was obtained previously by the reaction of *o*-fluorobenzoyl chloride with ethyl trifluoroacetoacetate in the presence of sodium hydride[25] as well as from salicyloylacetic acid ester, which was condensed with trifluoroacetic anhydride in the presence of K_2CO_3 in refluxing toluene.[26] This ester is an important intermediate to a class of therapeutics for the treatment of inflammation.[26]

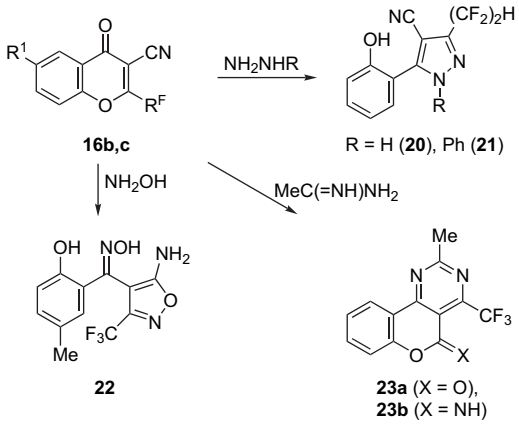
In marked contrast to the known 3-cyanochromones, 3-cyano-2-CF_3-chromones **16a**,**b** under the reaction conditions that had been used for the preparation of 2-amino-3-formylchromone[19b,3d] were prone to the facile detrifluoroacetylation to give either 2-aminochromones **17a**,**b** with morpholine or salicyloylacetonitriles **19a**,**b** with NaOH. The latter readily isomerize on heating into **17**.[21] The transformation **16**→**19** also occurs in aqueous DMSO through intermediate **16′**, which was detected in the ^{1}H and ^{13}C NMR spectra of **16b** in DMSO-d_6. Spectral data and melting points of **17a**,**b** and **19a**,**b** were consistent with previous reports.[21,27,28] The expected products, 2-amino-3-(trifluoroacetyl)chromones **16″**, were not obtained, a result, which reflects the ease with which chromones **16** undergo detrifluoroacetylation (Scheme 10).



Scheme 10.

When chromone **16a** was treated with an excess of aniline under solvent-free conditions or in ethanol at 80–90 °C for 2–3 h, only unchanged starting material was recovered; **16a** is dissolved in 25% NH_3, but does not react with it at room temperature for 15 min. The reactions of **16a** with benzylamine, pyrrolidine, and piperidine at reflux in methanol were accompanied by cleavage of the chromone system and were not examined more closely.

To demonstrate the ability of compounds **16** to undergo heterocyclization reactions, chromones **16b**,**c** as representative examples were allowed to react with hydrazines and hydroxylamine in refluxing methanol for 2–3 h. Our preliminary results showed that **16c** smoothly reacted with hydrazine and phenylhydrazine to produce the expected pyrazoles **20** and **21** in 31 and 98% yields, respectively. Unlike hydrazines, hydroxylamine hydrochloride (2 equiv) in the presence of AcONa reacted with **16b** to give 5-aminoisoxazole oxime **22** in 47% yield. In conjunction with the pharmaceutical importance known for fused heterocycles incorporating a coumarin moiety,[29,30] it should be noted that the conjugate addition of acetamidine hydrochloride also took place under weakly acidic conditions (AcONa) in refluxing DMF for 15 min to give a 73:27 mixture of 2,9-dimethyl-4-(trifluoromethyl)-5*H*-chromeno[4,3-*d*]pyrimidin-5-one **23a** and imine derivative **23b**, indicating that partial hydrolysis of **23b** had occurred. When this mixture was treated with aqueous AcOH, analytically pure coumarin **23a** was obtained (Scheme 11). The structures have been arrived at by detailed spectroscopic analysis and comparison of the spectroscopic data with the data reported for related systems.[29,31,32]



Scheme 11.

We believe that these reactions proceed through common intermediate formed by the attack of the NH_2 group at the C-2 atom with pyrone ring-opening. Further, in the case of hydrazines, the intramolecular heterocyclization occurs between the C=O and NHR groups to produce pyrazoles **20** and **21**. In the case of hydroxylamine, additions of the second NH_2OH molecule to the aroyl carbonyl and oxime hydroxyl to the cyano group give 5-aminoisoxazole **22**. Reaction with acetamidine includes two intramolecular cyclizations at the keto and cyano groups to form a tricyclic imino intermediate **23b**, which is subsequently followed by hydrolysis to **23a**. Similar non-fluorinated products are reported by Trimeche et al.[31] in the synthesis of 5*H*-chromeno[4,3-*d*]pyrimidin-5-ones using chromeno[4,3-*b*][1,5]benzodiazepin-7(8*H*)-ones and substituted amidines in the presence of triethylamine.

Thus, the initial Michael addition to **16** leads to three different types of products, depending on the nature of a bidentate nucleophile. These results clearly indicate that the C-2 atom of chromones **16** is very susceptible to nucleophilic attack and make them an attractive building block for the synthesis of various heterocycles containing the R^F group. An investigation of the reactivity of 3-cyano-2-R^F-chromones is now in progress.

3. Conclusion

In conclusion, we have shown, for the first time, that the reaction of 3-(polyfluoroacyl)chromones with hydroxylamine occurs mainly as nucleophilic 1,4-addition and provides a simple and practical method for the introduction of CN and $CONH_2$ groups at

the 3-position of 2-(polyfluoroalkyl)chromones. The resulting 3-cyano- and 3-carbamoyl-2-(polyfluoroalkyl)chromones are of considerable interest as reactive precursors in the synthesis of other useful organic materials containing polyfluoroalkyl groups. In addition, oximation of 3-(polyfluoroacyl)chromones with hydroxylamine hydrochloride depending on the nature of the substituents results in the formation of chromone 3-oxime and 4-salicyloylisoxazole derivatives. The observed difference in reactivity between 3-R^FCO-chromones and the non-fluorinated 3-RCO-chromones is undoubtedly due to the presence of the powerful electron-withdrawing R^F group in place of H, Me or Ph on the 3-acyl moiety, by which the electron density is reduced considerably, thus facilitating the reactions with nucleophilic reagents.

4. Experimental section

4.1. General

^{1}H (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. Assignment of chemical shifts was based on standard 2D NMR techniques (^{1}H–^{13}C HSQC and HMBC). IR spectra were recorded on a Perkin–Elmer Spectrum BX-II instrument as KBr discs. Electron impact mass spectra were obtained on a Perkin–Elmer model GC–MS instrument. 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 chromones **6a**–**f**,**h**,**i**,**k** were prepared according to described procedure.[9b,10c]

4.1.1. 6-Nitro-3-(2,2,3,3-tetrafluoropropionyl)chromone (**6g**)

A mixture of concentrated H_2SO_4 (2 mL), 96% HNO_3 (2 mL), and chromone **6c** (1.0 g, 3.65 mmol) was heated at 75 °C for 1.5 h. After cooling, the reaction mixture was poured with stirring onto crushed ice (20 g). The precipitate formed was filtered, washed with water, dried, and recrystallized from a toluene–hexane (1:3) mixture to give **6g** as colorless crystals. Yield 52%, mp 93–95 °C; IR (KBr) 3438, 3100, 3075, 1701, 1680, 1627, 1566, 1534, 1348 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.68 (tt, 1H, CF_2CF_2H, $^2J_{H,F}$=53.0 Hz, $^3J_{H,F}$=5.7 Hz), 7.76 (d, 1H, H-8, J=9.2 Hz), 8.59 (s, 1H, H-2), 8.62 (dd, 1H, H-7, J=9.2, 2.8 Hz), 9.13 (d, 1H, H-5, J=2.8 Hz); hydrate form (25%) δ 6.03 (s, 2H, 2OH), 6.28 (tt, 1H, CF_2CF_2H, $^2J_{H,F}$=52.9 Hz, $^3J_{H,F}$=6.2 Hz), 7.75 (d, 1H, H-8, J=9.2 Hz), 8.43 (s, 1H, H-2), 8.61 (dd, 1H, H-7, J=9.2, 2.8 Hz), 9.10 (d, 1H, H-5, J=2.8 Hz). The same nitrating mixture was used for the preparation of chromone **6j**[9b] from **6a**, yield 55%.

4.2. General procedures for the synthesis of 4-(polyfluoroalkyl)-4*H*-chromeno[3,4-*d*]isoxazol-4-ols (9a–h)

Method A. To a solution of hydroxylamine, prepared from $NH_2OH\cdot HCl$ (1.0 mmol) and KOH (0.9 mmol) in MeOH (3 mL), 3-R^FCO-chromone **6** (0.5 mmol) was added. The resulting mixture was allowed to stand for 18–24 h at room temperature and then diluted with water (5–8 mL) containing AcOH (1.5 mmol). After cooling, the precipitate formed was filtered, washed with water, dried, and recrystallized from a toluene–hexane (1:1) mixture to give **9** as colorless crystals.

Method B. To a hot solution of $NH_2OH\cdot HCl$ (1.0 mmol) and AcONa (1.0 mmol) in MeOH (3 mL), 3-R^FCO-chromone **6** (0.5 mmol) was added. The resulting mixture was allowed to stand for 3 days at room temperature and then diluted with water (5–8 mL). After cooling, the precipitate formed was filtered, washed with water, dried, and recrystallized from a toluene–hexane (1:1) mixture to give **9** as colorless crystals.

4.2.1. 4-(Trifluoromethyl)-4H-chromeno[3,4-d]isoxazol-4-ol (**9a**)

Yield 72%, mp 144–145 °C; IR (KBr) 3105, 1651, 1608, 1573, 1515, 1470, 1454 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.12 (br s, 1H, OH), 7.17–7.22 (m, 2H, H-6, H-8), 7.47 (ddd, 1H, H-7, J=8.5, 7.6, 1.6 Hz), 7.77 (dd, 1H, H-9, J=7.6, 1.6 Hz), 8.40 (s, 1H, H-3); ^{19}F NMR (376 MHz, $CDCl_3$, HFB) δ 76.47 (d, CF_3, J=0.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 95.6 (q, *C*–CF_3, $^2J_{C,F}$=36.3 Hz), 104.2, 110.5, 117.2, 121.4 (q, CF_3, $^1J_{C,F}$=285.7 Hz), 122.6, 123.3, 133.0, 146.6, 151.3, 163.3. Anal. Calcd for $C_{11}H_6F_3NO_3$: C, 51.38; H, 2.35; N, 5.45. Found: C, 51.09; H, 2.12; N, 5.46.

4.2.2. 8-Methyl-4-(trifluoromethyl)-4H-chromeno[3,4-d]isoxazol-4-ol (**9b**)

Yield 65%, mp 143–144 °C; IR (KBr) 3109, 1652, 1611, 1580, 1509, 1482, 1457 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.39 (s, 3H, Me), 3.90 (br s, 1H, OH), 7.07 (d, 1H, H-6, J=8.5 Hz), 7.27 (ddq, 1H, H-7, J=8.5, 2.2 Hz, $^4J_{H,Me}$=0.6 Hz), 7.57 (br d, 1H, H-9, J=2.0 Hz), 8.39 (q, 1H, H-3, $^5J_{H,F}$=0.8 Hz); ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.35 (s, 3H, Me), 7.16 (d, 1H, H-6, J=8.5 Hz), 7.36 (dd, 1H, H-7, J=8.5, 2.1 Hz), 7.63 (br d, 1H, H-9, J=2.0 Hz), 9.00 (s, 1H, H-3), 9.43 (s, 1H, OH). Anal. Calcd for $C_{12}H_8F_3NO_3$: C, 53.15; H, 2.97; N, 5.16. Found: C, 53.22; H, 2.85; N, 5.44.

4.2.3. 4-(1,1,2,2-Tetrafluoroethyl)-4H-chromeno[3,4-d]isoxazol-4-ol (**9c**)

Yield 70%, mp 105–106 °C; IR (KBr) 3142, 1643, 1607, 1572, 1513, 1468, 1456 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.50 (br s, 1H, OH), 6.22 (tdd, 1H, CF_2CF_2H, $^2J_{H,F}$=52.7 Hz, $^3J_{H,F}$=7.7, 4.3 Hz), 7.16 (d, 1H, H-6, J=8.3 Hz), 7.20 (td, 1H, H-8, J=7.6, 1.0 Hz), 7.46 (ddd, 1H, H-7, J=8.3, 7.5, 1.6 Hz), 7.74 (dd, 1H, H-9, J=7.7, 1.6 Hz), 8.36 (d, 1H, H-3, $^5J_{H,F}$=1.1 Hz); ^{19}F NMR (376 MHz, $CDCl_3$, HFB) δ 24.34 (dddd, C*F*FH, $^2J_{F,F}$=306.0 Hz, $^2J_{F,H}$=52.7 Hz, $^3J_{F,F}$=10.8, 6.0 Hz), 26.80 (dddd, CF*F*H, $^2J_{F,F}$=306.0 Hz, $^2J_{F,H}$=52.7 Hz, $^3J_{F,F}$=11.5, 1.4 Hz), 30.67 (ddd, C*F*F, $^2J_{F,F}$=272.5 Hz, $^3J_{F,F}$=10.8 Hz, $^3J_{F,H}$=4.3 Hz), 32.61 (ddt, CF*F*, $^2J_{F,F}$=272.5 Hz, $^3J_{F,F}$=11.5 Hz, $^3J_{F,H}\approx{}^3J_{F,F}\approx$6.8 Hz). Anal. Calcd for $C_{12}H_7F_4NO_3$: C, 49.84; H, 2.44; N, 4.84. Found: C, 49.84; H, 2.45; N, 4.90.

4.2.4. 8-Methyl-4-(1,1,2,2-tetrafluoroethyl)-4H-chromeno-[3,4-d]isoxazol-4-ol (**9d**)

Yield 57%, mp 117–118 °C; IR (KBr) 3224, 1650, 1609, 1579, 1508, 1509, 1482, 1452 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.39 (s, 3H, Me), 4.08 (br s, 1H, OH), 6.20 (tdd, 1H, CF_2CF_2H, $^2J_{H,F}$=52.6 Hz, $^3J_{H,F}$=7.7, 4.3 Hz), 7.04 (d, 1H, H-6, J=8.5 Hz), 7.26 (ddq, 1H, H-7, J=8.5, 2.2 Hz, $^4J_{H,Me}$=0.6 Hz), 7.57 (br d, 1H, H-9, J=2.0 Hz), 8.39 (t, 1H, H-3, $^5J_{H,F}$=1.1 Hz). Anal. Calcd for $C_{13}H_9F_4NO_3$: C, 51.50; H, 2.99; N, 4.62. Found: C, 51.25; H, 3.05; N, 4.71.

4.2.5. 7,9-Dimethyl-4-(1,1,2,2-tetrafluoroethyl)-4H-chromeno-[3,4-d]isoxazol-4-ol (**9e**)

This compound was obtained as a mixture with 5,7-dimethyl-4-oxo-2-(1,1,2,2-tetrafluoroethyl)-4*H*-chromene-3-carbonitrile (**16e**), total yield 40% (methods A and B), mp 135–140 °C (toluene–hexane, 3:1); ^{1}H NMR (400 MHz, DMSO-d_6) δ (**9e**, 75%) 2.31 (s, 3H, Me-7), 2.62 (s, 3H, Me-9), 6.76 (tt, 1H, CF_2CF_2H, $^2J_{H,F}$=51.7 Hz, $^3J_{H,F}$=6.6 Hz), 6.85 (s, 1H, H-6), 6.88 (s, 1H, H-8), 8.86 (s, 1H, H-3), 9.22 (s, 1H, OH); (**16e**, 25%) 2.44 (s, 3H, Me-7), 2.72 (s, 3H, Me-5), 7.05 (tt, 1H, CF_2CF_2H, $^2J_{H,F}$=51.4 Hz, $^3J_{H,F}$=4.4 Hz), 7.29 (s, 1H, H-6), 7.45 (s, 1H, H-8).

4.2.6. 8-Chloro-4-(trifluoromethyl)-4H-chromeno[3,4-d]isoxazol-4-ol (**9f**)

Yield 54%, mp 125–126 °C; IR (KBr) 3121, 1648, 1604, 1563, 1510, 1509, 1467 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.24 (br s, 1H, OH),

7.13 (d, 1H, H-6, J=8.9 Hz), 7.42 (dd, 1H, H-7, J=8.9, 2.5 Hz), 7.74 (br d, 1H, H-9, J=2.5 Hz), 8.41 (q, 1H, H-3, $^5J_{H,F}$=0.6 Hz); ^{19}F NMR (376 MHz, $CDCl_3$, HFB) δ 76.52 (s, CF_3). Anal. Calcd for $C_{11}H_5ClF_3NO_3$: C, 45.31; H, 1.73; N, 4.80. Found: C, 45.56; H, 1.68; N, 4.89.

4.2.7. 8-Nitro-4-(1,1,2,2-tetrafluoroethyl)-4H-chromeno-[3,4-d]isoxazol-4-ol (**9g**)

Yield 51% (method B), 24% (method A), mp 124–125 °C; IR (KBr) 3123, 1660, 1621, 1578, 1528, 1510, 1471 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.65 (br s, 1H, OH), 6.22 (tdd, 1H, CF_2CF_2H, $^2J_{H,F}$=52.5 Hz, $^3J_{H,F}$=7.3, 4.1 Hz), 7.30 (d, 1H, H-6, J=9.0 Hz), 8.35 (dd, 1H, H-7, J=9.1, 2.7 Hz), 8.48 (t, 1H, H-3, $^5J_{H,F}$=1.0 Hz), 8.68 (d, 1H, H-9, J=2.7 Hz); MS (EI): m/z (%) 316 $[M-H_2O]^+$ (57), 286 $[M-H_2O-NO]^+$ (23), 270 $[M-H_2O-NO_2]^+$ (28), 191 (42), 107 (31), 75 (100), 63 (44), 51 (36). Anal. Calcd for $C_{12}H_6F_4N_2O_5$: C, 43.13; H, 1.81; N, 8.38. Found: C, 43.10; H, 1.68; N, 8.47.

4.2.8. 4-(Trichloromethyl)-4H-chromeno[3,4-d]isoxazol-4-ol (**9h**)

Yield 10%, mp 156–157 °C (toluene–heptane); IR (KBr) 3107, 1649, 1606, 1574, 1514, 1468, 1451 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.18–7.23 (m, 2H, H-6, H-8), 7.53 (ddd, 1H, H-7, J=8.4, 7.4, 1.7 Hz), 7.80 (dd, 1H, H-9, J=7.9, 1.7 Hz), 9.05 (s, 1H, H-3), 9.53 (s, 1H, OH). Anal. Calcd for $C_{11}H_6Cl_3NO_3$: C, 43.10; H, 1.97; N, 4.57. Found: C, 43.34; H, 2.12; N, 4.42.

4.2.9. 5-(Difluoromethyl)-4-salicyloylisoxazole (**10i**)

Yield 55% (method A), 20% (method B), mp 94–95 °C, pale yellow crystals; IR (KBr) 1627, 1601, 1488, 1450 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (ddd, 1H, H-5′, J=8.2, 7.2, 1.1 Hz), 7.03 (t, 1H, CF_2H, $^2J_{H,F}$=52.2 Hz), 7.11 (dd, 1H, H-3′, J=8.4, 1.1 Hz), 7.57 (dd, 1H, H-6′, J=8.1, 1.6 Hz), 7.61 (ddd, 1H, H-4′, J=8.4, 7.2, 1.6 Hz), 8.62 (t, 1H, H-3, $^5J_{H,F}$=1.5 Hz), 11.49 (s, 1H, OH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.98 (td, 1H, H-5′, J=7.5, 1.0 Hz), 7.02 (dd, 1H, H-3′, J=7.8, 1.0 Hz), 7.41 (t, 1H, CF_2H, $^2J_{H,F}$=51.5 Hz), 7.52 (td, 1H, H-4′, J=7.6, 1.6 Hz), 7.54 (dd, 1H, H-6′, J=7.7, 1.6 Hz), 9.08 (t, 1H, H-3, $^5J_{H,F}$=1.7 Hz), 10.72 (s, 1H, OH); ^{19}F NMR (376 MHz, DMSO-d_6, HFB) δ 43.66 (dd, CF_2H, $^2J_{F,H}$=51.5 Hz, $^5J_{F,H}$=1.7 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 106.9 (t, CF_2H, $^1J_{C,F}$=238.1 Hz), 117.3 (C-3′), 119.5 (C-5′), 121.2 (t, C-4, $^3J_{C,F}$=4.6 Hz), 123.9 (C-1′), 130.7 (C-6′), 135.3 (C-4′), 151.4 (C-3), 157.7 (C-2′), 162.6 (t, C-5, $^2J_{C,F}$=25.4 Hz), 186.9 (C=O); MS (EI): m/z (%) 239 $[M]^+$ (12), 188 $[M-CF_2H]^+$ (92), 121 $[HOC_6H_4CO]^+$ (100), 93 $[HOC_6H_4]^+$ (24), 77 $[C_6H_5]^+$ (17), 65 $[C_5H_5]^+$ (46), 51 $[CF_2H]^+$ (34). Anal. Calcd for $C_{11}H_7F_2NO_3$: C, 55.24; H, 2.95; N, 5.86. Found: C, 55.10; H, 2.89; N, 6.08.

4.2.10. [5-(Difluoromethyl)isoxazol-4-yl](2′-hydroxyphenyl)-methanone oxime (**11i**)

This compound was detected in a mixture with **10i** and was not obtained in a pure form. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.88 (td, 1H, H-5′, J=7.5, 1.0 Hz), 6.91 (dd, 1H, H-3′, J=7.7, 1.0 Hz), 7.13 (t, 1H, CF_2H, $^2J_{H,F}$=52.0 Hz), 7.18 (dd, 1H, H-6′, J=7.7, 1.6 Hz), 7.30 (ddd, 1H, H-4′, J=7.7, 7.3, 1.6 Hz), 8.88 (t, 1H, H-3, $^5J_{H,F}$=1.5 Hz), 10.28 (s, 1H, OH), 12.24 (s, 1H, NOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.77 (t, 1H, CF_2H, $^2J_{H,F}$=52.9 Hz), 6.88 (ddd, 1H, H-5′, J=7.9, 7.2, 1.1 Hz), 6.96 (dd, 1H, H-6′, J=7.9, 1.7 Hz), 7.05 (dd, 1H, H-3′, J=8.3, 1.1 Hz), 7.34 (ddd, 1H, H-4′, J=8.3, 7.2, 1.7 Hz), 8.00 (s, 1H, OH), 8.36 (t, 1H, H-3, $^5J_{H,F}$=1.4 Hz), 10.31 (s, 1H, NOH).

4.2.11. (2′-Hydroxy-5′-nitrophenyl)[5-(1,1,2,2-tetrafluoroethyl)-isoxazol-4-yl]methanone oxime (**11g**)

A mixture of chromone **6g** (150 mg, 0.47 mmol) and $NH_2OH\cdot HCl$ (130 mg, 1.9 mmol) in MeOH (5 mL) was refluxed for 5 h. After cooling, the resulting mixture was diluted with water (15 mL). The solid product was collected by filtration, dried, and recrystallized from toluene to give **11g** as pale yellow crystals. Yield 37%, mp 206–207 °C; IR (KBr) 3316, 1655, 1630, 1609, 1580, 1514, 1485 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.88 (tt, 1H, HCF_2CF_2, $^2J_{H,F}$=51.6 Hz, $^3J_{H,F}$=4.1 Hz), 7.02 (d, 1H, H-3′, J=9.0 Hz), 8.16 (d, 1H, H-6′, J=2.9 Hz), 8.20 (dd, 1H, H-4′, J=9.0, 2.9 Hz), 9.10 (t, 1H, H-3, $^5J_{H,F}$=1.1 Hz), 11.54 (s, 1H, OH), 12.49 (s, 1H, NOH); MS (EI): m/z (%) 331 $[M-H_2O]^+$ (100), 301 $[M-H_2O-NO]^+$ (55), 280 $[M-H_2O-CHF_2]^+$ (44), 257 (32), 230 $[M-H_2O-C_2HF_4]^+$ (28), 202 (50), 156 (27), 101 (44), 76 (55), 63 (52), 51 (68), 30 (47). Anal. Calcd for $C_{12}H_7F_4N_3O_5$: C, 41.27; H, 2.02; N, 12.03. Found: C, 41.57; H, 1.90; N, 11.94.

4.2.12. (2′-Hydroxy-5′-nitrophenyl)[5-(trifluoromethyl)isoxazol-4-yl]methanone oxime (**11j**)

This compound was obtained from chromone **6j** as described for **11g**. Yield 70%, mp 228–230 °C (decomp.); IR (KBr) 3324, 1632, 1609, 1579, 1512, 1483 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.03 (d, 1H, H-3′, J=9.0 Hz), 8.22 (dd, 1H, H-4′, J=9.0, 2.9 Hz), 8.25 (d, 1H, H-6′, J=2.9 Hz), 9.11 (q, 1H, H-3, $^5J_{H,F}$=0.9 Hz), 11.56 (s, 1H, OH), 12.58 (s, 1H, NOH); ^{19}F NMR (376 MHz, DMSO-d_6, HFB) δ 99.63 (d, CF_3, $^5J_{F,H}$=0.9 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 113.5 (q, C-4, $^3J_{C,F}$=2.2 Hz), 116.9 (C-3′), 118.0 (q, CF_3, $^1J_{C,F}$=270.5 Hz), 121.6 (C-1′), 125.3 (C-6′), 126.9 (C-4′), 139.6 (C-5′), 141.3 (C=N), 152.1 (C-3), 152.4 (q, C-5, $^2J_{C,F}$=41.1 Hz), 161.8 (C-2′); MS (EI): m/z (%) 317 $[M]^+$ (83), 299 $[M-H_2O]^+$ (49), 269 $[M-H_2O-NO]^+$ (28), 248 $[M-CF_3]^+$ (100), 202 (29), 108 (57), 79 (56), 69 $[CF_3]^+$ (88), 63 (72), 53 (44). Anal. Calcd for $C_{11}H_6F_3N_3O_5$: C, 41.65; H, 1.91; N, 13.25. Found: C, 41.33; H, 1.87; N, 13.05.

4.2.13. 3-(2′-Hydroxy-5′-nitrophenyl)-3-oxopropanal dioxime (**12**)

Yield 34% (method A), 40% (method B), mp 217–218 °C, yellow crystals; IR (KBr) 3317, 3216, 3097, 2930, 1628, 1609, 1579, 1509, 1485, 1388, 1324 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) *syn*-isomer (55%) δ 3.76 (d, 2H, CH_2, J=5.1 Hz), 6.71 (t, 1H, CH=N, J=5.1 Hz), 7.07 (d, 1H, H-3′, J=9.0 Hz), 8.16 (dd, 1H, H-4′, J=9.0, 2.8 Hz), 8.27 (d, 1H, H-6′, J=2.8 Hz), 11.16 (br s, 1H, OH), 11.7–12.5 (br s, 2H, 2NOH); *anti*-isomer (40%) δ 3.73 (d, 2H, CH_2, J=5.1 Hz), 7.08 (d, 1H, H-3′, J=9.0 Hz), 7.39 (t, 1H, CH=N, J=5.1 Hz), 8.15 (dd, 1H, H-4′, J=9.0, 2.8 Hz), 8.25 (d, 1H, H-6′, J=2.8 Hz), 10.69 (s, 1H, OH), 11.7–12.5 (br s, 2H, 2NOH). *3-(2′-Hydroxy-5′-nitrophenyl)-5-(hydroxyamino)-4,5-dihydroisoxazole* **13** (5%) δ 3.25 (dd, 1H, *CH*H, J=18.0, 4.7 Hz), 3.57 (dd, 1H, CH*H*, J=18.0, 9.8 Hz), 5.55 (br dd, 1H, CH, $J\approx$10.0, 5.0 Hz), 6.55 (br s, 1H, NH), 7.13 (d, 1H, H-3′, J=9.1 Hz), 7.51 (br s, 1H, OH), 8.19 (dd, 1H, H-4′, J=9.1, 2.9 Hz), 8.36 (d, 1H, H-6′, J=2.9 Hz), 11.7–12.5 (br s, 2H, 2OH). Anal. Calcd for $C_9H_9N_3O_5$: C, 45.19; H, 3.79; N, 17.57. Found: C, 45.06; H, 3.52; N, 17.39.

4.3. General procedure for chromone 3-oximes 14b,c,i,k

Method C. To a heterogeneous mixture of 3-R^FCO-chromone **6** (1.0 mmol) and $NH_2OH\cdot HCl$ (84 mg, 1.2 mmol) in methanol or ethanol (4 mL) was added one drop of concentrated HCl. The mixture was refluxed for 5 h, concentrated to dryness, diluted with hot water, and then extracted with benzene. The solvent was evaporated and the crude solid was recrystallized from a toluene–hexane (1:1) mixture to give **14** as colorless crystals.

4.3.1. 1-(6-Methyl-4-oxo-4H-chromen-3-yl)-2,2,2-trifluoroethan-1-one oxime (**14b**)

Yield 28%, mp 202–203 °C; IR (KBr) 3223, 1650, 1628, 1574, 1487 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.47 (s, 3H, Me), 7.41 (d, 1H, H-8, J=8.6 Hz), 7.55 (ddq, 1H, H-7, J=8.6, 2.2 Hz, $^4J_{H,Me}$=0.6 Hz), 7.97 (s, 1H, H-2), 8.05 (br d, 1H, H-5, J=2.0 Hz), 8.69 (s, 1H, OH); ^{19}F NMR (376 MHz, $CDCl_3$, HFB) δ 93.42 (d, CF_3, J=0.5 Hz); MS (EI): m/z (%) 271 $[M]^+$ (100), 221 (41), 135 $[HO(Me)C_6H_3CO]^+$ (75), 134 $[O(Me)C_6H_3CO]^+$ (100), 107 $[MeC_6H_3OH]^+$ (48), 106 $[MeC_6H_3O]^+$ (80), 77 $[C_6H_5]^+$ (100), 69 $[CF_3]^+$ (100), 51 $[C_4H_3]^+$ (87), 39 (62), 29

(44). Anal. Calcd for $C_{12}H_8F_3NO_3$: C, 53.15; H, 2.97; N, 5.16. Found: C, 52.77; H, 3.07; N, 4.99.

*4.3.2. 1-(4-Oxo-4H-chromen-3-yl)-2,2,3,3-tetrafluoropropan-1-one oxime (**14c**)*

Yield 24%, mp 186–187 °C; IR (KBr) 3225, 1649, 1622, 1602, 1570, 1465 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.30 (tt, 1H, CF_2CF_2H, $^2J_{H,F}$=52.8 Hz, $^3J_{H,F}$=5.3 Hz), 7.48 (ddd, 1H, H-6, J=7.9, 7.3, 0.9 Hz), 7.53 (d, 1H, H-8, J=8.4 Hz), 7.75 (ddd, 1H, H-7, J=8.6, 7.2, 1.7 Hz), 8.01 (s, 1H, H-2), 8.26 (dd, 1H, H-5, J=8.0, 1.6 Hz), 8.78 (s, 1H, OH); ^1H NMR (400 MHz, DMSO-d_6) δ 6.85 (t, 1H, CF_2CF_2H, $^2J_{H,F}$=51.6 Hz, $^3J_{H,F}$=5.8 Hz), 7.57 (ddd, 1H, H-6, J=8.0, 7.1, 1.1 Hz), 7.73 (dd, 1H, H-8, J=8.5, 1.1 Hz), 7.89 (ddd, 1H, H-7, J=8.5, 7.1, 1.7 Hz), 8.08 (dd, 1H, H-5, J=8.0, 1.7 Hz), 8.50 (s, 1H, H-2), 12.86 (s, 1H, OH). Anal. Calcd for $C_{12}H_7F_4NO_3$: C, 49.84; H, 2.44; N, 4.84. Found: C, 49.73; H, 2.46; N, 4.74.

*4.3.3. 1-(4-Oxo-4H-chromen-3-yl)-2,2-difluoroethan-1-one oxime (**14i**)*

Yield 45%, mp 166–167 °C; IR (KBr) 3203, 1665, 1620, 1603, 1568, 1468 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.47 (t, 1H, CF_2H, $^2J_{H,F}$=54.7 Hz), 7.47 (ddd, 1H, H-6, J=8.0, 7.2, 1.1 Hz), 7.52 (dd, 1H, H-8, J=8.5, 1.0 Hz), 7.74 (ddd, 1H, H-7, J=8.6, 7.2, 1.7 Hz), 8.10 (s, 1H, H-2), 8.27 (dd, 1H, H-5, J=8.0, 1.6 Hz), 8.85 (br s, 1H, OH); ^1H NMR (400 MHz, DMSO-d_6) δ 6.74 (t, 1H, CF_2H, $^2J_{H,F}$=54.2 Hz), 7.57 (ddd, 1H, H-6, J=8.0, 7.1, 1.1 Hz), 7.72 (ddd, 1H, H-8, J=8.5, 1.1, 0.5 Hz), 7.88 (ddd, 1H, H-7, J=8.5, 7.1, 1.7 Hz), 8.09 (ddd, 1H, H-5, J=8.0, 1.7, 0.5 Hz), 8.47 (s, 1H, H-2), 12.44 (s, 1H, OH); ^{19}F NMR (376 MHz, DMSO-d_6, HFB) δ 45.02 (d, CF_2H, $^2J_{F,H}$=54.2 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 113.2 (t, CF_2H, $^1J_{C,F}$=235.8 Hz), 114.0 (C-3), 118.6 (C-8), 123.3 (C-4a), 125.2 (C-5), 126.1 (C-6), 134.8 (C-7), 143.3 (t, C=N, $^2J_{C,F}$=27.6 Hz), 155.6 (C-8a), 155.8 (C-2), 172.9 (C-4). Anal. Calcd for $C_{11}H_7F_2NO_3$: C, 55.24; H, 2.95; N, 5.86. Found: C, 55.48; H, 2.89; N, 5.75.

*4.3.4. 1-(6-Chloro-4-oxo-4H-chromen-3-yl)-2,2-difluoroethan-1-one oxime (**14k**)*

Yield 35%, mp 181–182 °C; IR (KBr) 3246, 1662, 1632, 1613, 1566, 1466 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.45 (t, 1H, CF_2H, $^2J_{H,F}$=54.7 Hz), 7.49 (d, 1H, H-8, J=8.9 Hz), 7.68 (dd, 1H, H-7, J=8.9, 2.6 Hz), 8.07 (s, 1H, H-2), 8.22 (d, 1H, H-5, J=2.6 Hz), 8.74 (br s, 1H, OH); ^1H NMR (400 MHz, DMSO-d_6) δ 6.72 (t, 1H, CF_2H, $^2J_{H,F}$=54.1 Hz), 7.80 (dd, 1H, H-8, J=9.0, 0.3 Hz), 7.93 (dd, 1H, H-7, J=9.0, 2.6 Hz), 8.01 (dd, 1H, H-5, J=2.7, 0.3 Hz), 8.50 (s, 1H, H-2), 12.47 (s, 1H, OH); ^{19}F NMR (376 MHz, DMSO-d_6, HFB) δ 46.40 (d, CF_2H, $^2J_{F,H}$=54.0 Hz). Anal. Calcd for $C_{11}H_6ClF_2NO_3$: C, 48.29; H, 2.21; N, 5.12. Found: C, 48.43; H, 2.12; N, 5.13.

4.4. General procedure for 3-(polyfluoroalkyl)isoxazole 15b,c,i,k

A solution of oxime **14** (1.0 mmol) in DMSO (5 mL) was heated at 85 °C for 5 h. After cooling, the resulting mixture was diluted with water (15 mL) and the solid obtained was filtered and dried to give **15** as pink or pale yellow crystals.

*4.4.1. 4-(2-Hydroxy-5-methylbenzoyl)-3-(trifluoromethyl)-isoxazole (**15b**)*

Yield 62%, mp 106–107 °C; IR (KBr) 1636, 1613, 1592, 1573, 1489 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 2.26 (s, 3H, Me), 6.92 (d, 1H, H-3′, J=8.4 Hz), 7.34 (dd, 1H, H-4′, J=8.3, 2.3 Hz), 7.39 (d, 1H, H-6′, J=2.3 Hz), 9.82 (q, 1H, H-5, $^5J_{H,F}$=1.1 Hz), 10.38 (s, 1H, OH); MS (EI): m/z (%) 271 $[M]^+$ (100), 221 (38), 135 $[HO(Me)C_6H_3CO]^+$ (69), 134 $[O(Me)C_6H_3CO]^+$ (100), 107 $[MeC_6H_3OH]^+$ (46), 106 $[MeC_6H_3O]^+$ (77), 77 $[C_6H_5]^+$ (100), 69 $[CF_3]^+$ (97), 51 $[C_4H_3]^+$ (81), 39 (58), 29 (39). Anal. Calcd for $C_{12}H_8F_3NO_3$: C, 53.15; H, 2.97; N, 5.16. Found: C, 52.98; H, 3.13; N, 5.04.

*4.4.2. 4-Salicyloyl-3-(1,1,2,2-tetrafluoroethyl)isoxazole (**15c**)*

Yield 65%, mp 56–57 °C; IR (KBr) 1630, 1599, 1572, 1488, 1449 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 6.97 (ddd, 1H, H-5′, J=7.8, 7.3, 1.0 Hz), 7.01 (dd, 1H, H-3′, J=8.3, 0.8 Hz), 7.05 (tt, 1H, CF_2CF_2H, $^2J_{H,F}$=51.9 Hz, $^3J_{H,F}$=5.4 Hz), 7.52 (ddd, 1H, H-4′, J=8.3, 7.3, 1.7 Hz), 7.58 (dd, 1H, H-6′, J=7.8, 1.7 Hz), 9.78 (t, 1H, H-5, $^5J_{H,F}$=1.2 Hz), 10.62 (s, 1H, OH). Anal. Calcd for $C_{12}H_7F_4NO_3$: C, 49.84; H, 2.44; N, 4.84. Found: C, 49.98; H, 2.56; N, 4.88.

*4.4.3. 3-(Difluoromethyl)-4-salicyloylisoxazole (**15i**)*

Yield 70%, mp 84–85 °C; IR (KBr) 3100, 1630, 1605, 1575, 1568, 1493, 1445 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 6.98 (ddd, 1H, H-5′, J=7.8, 7.3, 0.8 Hz), 7.03 (dd, 1H, H-3′, J=8.2, 0.8 Hz), 7.46 (t, 1H, CF_2H, $^2J_{H,F}$=52.3 Hz), 7.51 (ddd, 1H, H-4′, J=8.2, 7.3, 1.7 Hz), 7.58 (dd, 1H, H-6′, J=7.8, 1.7 Hz), 9.71 (t, 1H, H-5, $^5J_{H,F}$=1.5 Hz), 10.65 (s, 1H, OH); ^{19}F NMR (376 MHz, DMSO-d_6, HFB) δ 43.59 (dd, CF_2H, $^2J_{F,H}$=52.3, $^5J_{F,H}$=1.5 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 109.0 (t, CF_2H, $^1J_{C,F}$=238.6 Hz), 117.3 (C-3′), 119.0 (t, C-4, $^3J_{C,F}$=1.7 Hz), 119.4 (C-5′), 124.1 (C-1′), 130.6 (C-6′), 134.8 (C-4′), 156.0 (t, C-3, $^2J_{C,F}$=24.9 Hz), 157.6 (C-2′), 166.3 (C-5), 187.2 (C=O). Anal. Calcd for $C_{11}H_7F_2NO_3$: C, 55.24; H, 2.95; N, 5.86. Found: C, 55.59; H, 3.16; N, 5.56.

*4.4.4. 4-(5′-Chloro-2′-hydroxybenzoyl)-3-(difluoromethyl)-isoxazole (**15k**)*

Yield 65%, mp 107–108 °C; IR (KBr) 3122, 3089, 1633, 1605, 1568, 1492, 1468 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.02 (m, 1H, H-3′), 7.44 (t, 1H, CF_2H, $^2J_{H,F}$=52.2 Hz), 7.48–7.52 (m, 2H, H-4′, H-6′), 9.72 (t, 1H, H-5, $^5J_{H,F}$=1.5 Hz), 10.68 (s, 1H, OH); ^{19}F NMR (376 MHz, DMSO-d_6, HFB) δ 43.45 (dd, CF_2H, $^2J_{F,H}$=52.2, $^5J_{F,H}$=1.5 Hz). Anal. Calcd for $C_{11}H_6ClF_2NO_3$: C, 48.29; H, 2.21; N, 5.12. Found: C, 48.07; H, 2.23; N, 4.90.

4.5. General procedure for the preparation of 4-oxo-2-(polyfluoroalkyl)-4*H*-chromene-3-carbonitriles (16a–e)

A solution of chromeno[3,4-*d*]isoxazol-4-ol **9** (1.0 mmol) in CF_3CO_2H (0.7 mL) was refluxed for 15 min. After cooling, the resulting mixture was diluted with water (4 mL). The precipitate formed was filtered, dried, and recrystallized from a toluene–hexane (1:1) mixture to give **16** as colorless crystals.

*4.5.1. 4-Oxo-2-(trifluoromethyl)-4H-chromene-3-carbonitrile (**16a**)*

Yield 84%, mp 119–120 °C; IR (KBr) 2245, 1667, 1637, 1610, 1580, 1468 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.62 (ddd, 1H, H-6, J=8.0, 7.3, 1.0 Hz), 7.64 (d, 1H, H-8, J=8.6 Hz), 7.89 (ddd, 1H, H-7, J=8.7, 7.2, 1.7 Hz), 8.28 (dd, 1H, H-5, J=8.0, 1.5 Hz); ^{19}F NMR (376 MHz, $CDCl_3$, HFB) δ 93.67 (s, CF_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 100.8, 108.8, 117.6 (q, CF_3, $^1J_{C,F}$=278.0 Hz), 118.7, 122.1, 126.4, 128.2, 136.5, 154.5, 158.0 (q, C-2, $^2J_{C,F}$=39.3 Hz), 171.8 (C=O); MS (EI): m/z (%) 239 $[M]^+$ (100), 170 $[M-CF_3]^+$ (60), 120 $[OC_6H_4CO]^+$ (100), 92 $[C_6H_4O]^+$ (100), 69 $[CF_3]^+$ (38), 64 $[C_5H_4]^+$ (73), 63 (76), 50 (72), 38 (39). Anal. Calcd for $C_{11}H_4F_3NO_2$: C, 55.24; H, 1.69; N, 5.86. Found: C, 55.20; H, 1.46; N, 5.87.

*4.5.2. 6-Methyl-4-oxo-2-(trifluoromethyl)-4H-chromene-3-carbonitrile (**16b**)*

Yield 72%, mp 149–150 °C; IR (KBr) 2239, 1680, 1631, 1484 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.52 (s, 3H, Me), 7.53 (d, 1H, H-8, J=8.6 Hz), 7.68 (dd, 1H, H-7, J=8.6, 2.2 Hz), 8.05 (br d, 1H, H-5, J=1.5 Hz); ^{19}F NMR (376 MHz, $CDCl_3$, HFB) δ 93.72 (s, CF_3); ^1H NMR (400 MHz, DMSO-d_6) (**16b**, 78%) δ 2.48 (s, 3H, Me), 7.79 (d, 1H, H-8, J=8.6 Hz), 7.83 (dd, 1H, H-7, J=8.6, 1.9 Hz), 7.92 (br s, 1H, H-5). *2,4-*

Dihydroxy-6-methyl-2-(trifluoromethyl)-2H-chromene-3-carbonitrile ***16′b*** (22%) δ 2.30 (s, 3H, Me), 6.98 (d, 1H, H-8, J=8.3 Hz), 7.31 (dd, 1H, H-7, J=8.3, 1.6 Hz), 7.56 (br s, 1H, H-5), 9.27 (br s, 1H, OH), 11.8–13.2 (br s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6) (**16b**) δ 20.4, 99.9, 110.3, 117.7 (q, CF_3, $^1J_{C,F}$=277.0 Hz), 118.7, 121.6, 124.5, 137.6, 138.2, 152.6, 157.1 (q, C-2, $^2J_{C,F}$=38.3 Hz), 172.6 (C=O); (**16′b**) δ 20.1, 77.0, 95.5 (q, C-2, $^2J_{C,F}$=33.2 Hz), 114.5, 115.1, 116.1, 122.1 (q, CF_3, $^1J_{C,F}$=290.0 Hz), 123.9, 131.5, 134.5, 150.1, 162.7. Anal. Calcd for $C_{12}H_6F_3NO_2$: C, 56.93; H, 2.39; N, 5.53. Found: C, 56.84; H, 2.21; N, 5.54.

4.5.3. 4-Oxo-2-(1,1,2,2-tetrafluoroethyl)-4H-chromene-3-carbonitrile (*16c*)

Yield 85%, mp 139–140 °C; IR (KBr) 2244, 1664, 1630, 1578, 1463 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.24 (tt, 1H, CF_2CF_2H, $^2J_{H,F}$=52.7 Hz, $^3J_{H,F}$=2.9 Hz), 7.61 (ddd, 1H, H-6, J=8.0, 7.3, 1.0 Hz), 7.62 (d, 1H, H-8, J=8.5 Hz), 7.88 (ddd, 1H, H-7, J=8.5, 7.2, 1.7 Hz), 8.28 (dd, 1H, H-5, J=8.0, 1.7 Hz); ^{19}F NMR (376 MHz, $CDCl_3$, HFB) δ 27.32 (dt, CF_2H, $^2J_{F,H}$=52.7 Hz, $^3J_{F,F}$=4.6 Hz), 43.78 (td, CF_2, $^3J_{F,F}$=4.6 Hz, $^3J_{F,H}$=3.0 Hz). Anal. Calcd for $C_{12}H_5F_4NO_2$: C, 53.15; H, 1.86; N, 5.17. Found: C, 53.16; H, 1.87; N, 5.21.

4.5.4. 6-Methyl-4-oxo-2-(1,1,2,2-tetrafluoroethyl)-4H-chromene-3-carbonitrile (*16d*)

Yield 71%, mp 187–188 °C; IR (KBr) 2243, 1665, 1627, 1484 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.48 (s, 3H, Me), 7.07 (tt, 1H, CF_2CF_2H, $^2J_{H,F}$=51.3 Hz, $^3J_{H,F}$=4.5 Hz), 7.73 (d, 1H, H-8, J=8.6 Hz), 7.82 (ddq, 1H, H-7, J=8.6, 2.2 Hz, $^4J_{H,Me}$=0.5 Hz), 7.94 (br d, 1H, H-5, J=1.5 Hz). Anal. Calcd for $C_{13}H_7F_4NO_2$: C, 54.75; H, 2.47; N, 4.91. Found: C, 54.44; H, 2.29; N, 4.77.

4.5.5. 5,7-Dimethyl-4-oxo-2-(1,1,2,2-tetrafluoroethyl)-4H-chromene-3-carbonitrile (*16e*)

Yield 73%, mp 167–168 °C; IR (KBr) 2238, 1662, 1639, 1615, 1562, 1481 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.47 (s, 3H, Me-7), 2.81 (s, 3H, Me-5), 6.19 (tt, 1H, CF_2CF_2H, $^2J_{H,F}$=52.8 Hz, $^3J_{H,F}$=3.0 Hz), 7.14 (s, 1H, H-6), 7.22 (s, 1H, H-8). Anal. Calcd for $C_{14}H_9F_4NO_2$: C, 56.20; H, 3.03; N, 4.68. Found: C, 56.21; H, 2.98; N, 4.79.

4.5.6. 4-Oxo-2-(difluoromethyl)-4H-chromene-3-carbonitrile (*16i*)

A solution of isoxazole **10i** (100 mg, 0.42 mmol) in DMSO (2.0 mL) was refluxed for 5 min. After cooling, the resulting mixture was diluted with water (10 mL). The precipitate formed was filtered, dried, and recrystallized from a toluene–hexane (1:4) mixture to give **16i** as colorless crystals. Yield 57%, mp 129–131 °C; IR (KBr) 2237, 1663, 1630, 1608, 1577, 1465 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.31 (t, 1H, CF_2H, $^2J_{H,F}$=51.4 Hz), 7.67 (ddd, 1H, H-6, J=8.0, 7.2, 1.0 Hz), 7.86 (dd, 1H, H-8, J=8.6, 1.0 Hz), 7.99 (ddd, 1H, H-7, J=8.6, 7.2, 1.7 Hz), 8.13 (dd, 1H, H-5, J=8.0, 1.7 Hz); ^{19}F NMR (376 MHz, DMSO-d_6, HFB) δ 39.74 (d, CF_2H, $^2J_{F,H}$=51.4 Hz). Anal. Calcd for $C_{11}H_5F_2NO_2$: C, 59.74; H, 2.28; N, 6.33. Found: C, 59.47; H, 2.34; N, 6.20.

4.5.7. 2-Amino-4H-chromen-4-one (*17a*)

This compound was prepared according to the procedure described previously.[19b] 3-Cyanochromone **16a** (100 mg, 0.42 mmol) was added to a mixture of morpholine (0.1 mL), DMF (0.14 mL), and water (0.5 mL) over a period of 5 min at 60 °C, and the mixture was stirred for 2 h at the same temperature. After the reaction mixture had been cooled with ice, the separated crystals were collected by filtration, washed with water, and dried to give **17a** as a yellow powder. Yield 60%, mp 270–272 °C (decomp.) (lit.[27] mp 268–270 °C (decomp.), lit.[28a] mp 275 °C (decomp.), lit.[28b] mp 274 °C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.18 (s, 1H, H-3), 7.35 (t, 1H, H-6, J=7.6 Hz), 7.37 (d, 1H, H-8, J=8.3 Hz), 7.51 (br s, 2H, NH_2), 7.60 (ddd, 1H, H-7, J=8.5, 7.3, 1.7 Hz), 7.90 (dd, 1H, H-5, J=7.8, 1.7 Hz).

4.5.8. 2-Amino-6-methyl-4H-chromen-4-one (*17b*)

A solution of chromeno[3,4-*d*]isoxazol-4-ol **9b** (100 mg, 0.37 mmol) and piperidine (130 mg, 1.53 mmol) in toluene (3 mL) was refluxed for 10 min, after which the solvent was partially evaporated. After cooling, the crystalline product was filtered and dried to give **17b** as yellow crystals. Yield 62%, mp>300 °C (lit.[21] mp 323–325 °C, lit.[28b] mp 320 °C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.37 (s, 3H, Me), 5.14 (s, 1H, H-3), 7.26 (d, 1H, H-8, J=8.4 Hz), 7.40 (dd, 1H, H-7, J=8.4, 2.0 Hz), 7.44 (br s, 2H, NH_2), 7.69 (d, 1H, H-5, J=2.0 Hz).

4.6. General procedure for the preparation of 4-oxo-2-(polyfluoroalkyl)-4*H*-chromene-3-carboxamides (18a–c,e,f)

Chromeno[3,4-*d*]isoxazol-4-ol **9** or 3-cyanochromone **16** (0.5 mmol) was added to concentrated H_2SO_4 (0.5 mL) and the mixture was left for 3 h at 90 °C. After cooling, the reaction mixture was diluted with water (5 mL) and the resulting crystalline product was filtered, washed with water, and dried to give **18** as a colorless powder.

4.6.1. 4-Oxo-2-(trifluoromethyl)-4H-chromene-3-carboxamide (*18a*)

Yield 80% from **9a** and 74% from **16a**, mp>250 °C (decomp.); IR (KBr) 3410, 3296, 1692, 1661, 1646, 1611, 1580, 1467 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.62 (ddd, 1H, H-6, J=8.0, 7.2, 1.0 Hz), 7.80 (d, 1H, H-8, J=8.5 Hz), 7.85 (br s, 1H, NH), 7.92 (br s, 1H, NH), 7.95 (ddd, 1H, H-7, J=8.5, 7.2, 1.7 Hz), 8.12 (dd, 1H, H-5, J=8.0, 1.6 Hz); ^{19}F NMR (376 MHz, DMSO-d_6, HFB) δ 95.61 (s, CF_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 118.6, 118.8 (q, CF_3, $^1J_{C,F}$=275.8 Hz), 122.7, 122.8 (q, C-3, $^3J_{C,F}$=1.7 Hz), 125.4, 126.9, 136.0, 146.2 (q, C-2, $^2J_{C,F}$=38.0 Hz), 154.5, 161.7, 174.4; MS (EI): m/z (%) 257 $[M]^+$ (88), 241 $[M-NH_2]^+$ (100), 214 $[M+1-CONH_2]^+$ (85), 166 (27), 121 $[HOC_6H_4CO]^+$ (41), 120 $[OC_6H_4CO]^+$ (34), 104 $[C_6H_4CO]^+$ (56), 92 $[C_6H_4O]^+$ (69), 69 $[CF_3]^+$ (24), 64 $[C_5H_4]^+$ (30), 63 (46), 50 (36), 44 $[CONH_2]^+$ (69). Anal. Calcd for $C_{11}H_6F_3NO_3$: C, 51.37; H, 2.35; N, 5.45. Found: C, 51.28; H, 2.34; N, 5.25.

4.6.2. 6-Methyl-4-oxo-2-(trifluoromethyl)-4H-chromene-3-carboxamide (*18b*)

Yield 75% from **9b**, mp 245–247 °C (decomp.); IR (KBr) 3387, 3285, 3189, 1693, 1656, 1618, 1599, 1484 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.46 (s, 3H, Me), 7.70 (d, 1H, H-8, J=8.6 Hz), 7.77 (br d, 1H, H-7, J=8.6 Hz), 7.83 (br s, 1H, NH), 7.90 (br s, 1H, H-5), 7.93 (br s, 1H, NH). Anal. Calcd for $C_{12}H_8F_3NO_3\cdot 0.25H_2O$: C, 52.28; H, 3.11; N, 5.08. Found: C, 52.38; H, 2.96; N, 4.87.

4.6.3. 4-Oxo-2-(1,1,2,2-tetrafluoroethyl)-4H-chromene-3-carboxamide (*18c*)

Yield 75% from **16c**, mp 180–181 °C; IR (KBr) ν 3391, 3305, 3190, 1694, 1658, 1614, 1574, 1467 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.97 (tt, 1H, CF_2CF_2H, $^2J_{H,F}$=51.7 Hz, $^3J_{H,F}$=5.5 Hz), 7.61 (ddd, 1H, H-6, J=8.0, 7.2, 1.0 Hz), 7.74 (d, 1H, H-8, J=8.5 Hz), 7.81 (br s, 1H, NH), 7.88 (br s, 1H, NH), 7.94 (ddd, 1H, H-7, J=8.5, 7.2, 1.7 Hz), 8.12 (dd, 1H, H-5, J=8.0, 1.6 Hz). Anal. Calcd for $C_{12}H_7F_4NO_3$: C, 49.84; H, 2.44; N, 4.84. Found: C, 49.47; H, 2.57; N, 4.87.

4.6.4. 5,7-Dimethyl-4-oxo-2-(1,1,2,2-tetrafluoroethyl)-4H-chromene-3-carboxamide (*18e*)

Yield 68% from **16e**, mp 200–203 °C (decomp.); IR (KBr) 3395, 3287, 3199, 1695, 1664, 1647, 1619, 1568, 1484 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.42 (s, 3H, 7-Me), 2.71 (s, 3H, 5-Me), 6.93 (tt, 1H, CF_2CF_2H, $^2J_{H,F}$=51.7 Hz, $^3J_{H,F}$=5.4 Hz), 7.19 (s, 1H, H-6), 7.35 (s, 1H, H-8), 7.74 (br s, 1H, NH), 7.84 (br s, 1H, NH). Anal. Calcd for $C_{14}H_{11}F_4NO_3$: C, 53.00; H, 3.49; N, 4.42. Found: C, 52.80; H, 3.41; N, 4.25.

*4.6.5. 6-Chloro-4-oxo-2-(trifluoromethyl)-4H-chromene-3-carboxamide (**18f**)*

Yield 77% from **9f**, mp 265–267 °C (decomp.); IR (KBr) 3370, 3277, 3196, 1692, 1660, 1608, 1599, 1470 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.88 (br s, 1H, NH), 7.89 (d, 1H, H-8, J=9.0 Hz), 7.92 (br s, 1H, NH), 8.00 (dd, 1H, H-7, J=9.0, 2.6 Hz), 8.06 (d, 1H, H-5, J=2.6 Hz). Anal. Calcd for $C_{11}H_5ClF_3NO_3$: C, 45.31; H, 1.73; N, 4.80. Found: C, 45.66; H, 1.54; N, 4.67.

*4.6.6. Salicyloylacetonitrile (**19a**)*

This compound was prepared according to the procedure described previously.[3d] 3-Cyanochromone **16a** (150 mg, 0.63 mmol) was added to a solution of NaOH (0.13 mg, 0.32 mmol) in water (0.6 mL) and the mixture was stirred for 2 h at 70 °C. After the reaction mixture had been cooled with ice, the separated crystals were collected by filtration, washed with water, and dried to give **19a** as yellow crystals. Yield 79%, mp 108–110 °C (lit.[27] mp 108–110 °C); ^1H NMR (400 MHz, $CDCl_3$) δ 4.14 (s, 2H, CH_2), 6.97 (t, 1H, H-5, J=7.7 Hz), 7.06 (d, 1H, H-3, J=8.2 Hz), 7.57 (d, 1H, H-6, J=7.8 Hz), 7.58 (t, 1H, H-4, J=7.5 Hz), 11.41 (s, 1H, OH).

*4.6.7. (2-Hydroxy-5-methylbenzoyl)acetonitrile (**19b**)*

A solution of chromone **16b** (100 mg, 0.4 mmol) in DMSO (2 mL) and water (1 mL) was allowed to stand for 4 days at room temperature and then diluted with water (6 mL). The solid obtained was filtered and dried to give **19b** as colorless crystals. Yield 65 mg (94%), mp 134–136 °C (lit.[21] mp 136–140 °C); ^1H NMR (400 MHz, DMSO-d_6) δ 2.24 (s, 3H, Me), 4.62 (s, 2H, CH_2), 6.90 (d, 1H, H-3, J=8.4 Hz), 7.34 (dd, 1H, H-4, J=8.4, 2.2 Hz), 7.54 (d, 1H, H-6, J=2.0 Hz), 10.91 (s, 1H, OH).

*4.6.8. 5-(2′-Hydroxyphenyl)-3-(1,1,2,2-tetrafluoroethyl)-1H-pyrazole-4-carbonitrile (**20**)*

A mixture of $N_2H_4 \cdot 2HCl$ (80 mg, 0.76 mmol) and KOH (60 mg, 1.1 mmol) in methanol (3 mL) was heated to reflux for 5 min and then 3-cyanochromone **16c** (100 mg, 0.37 mmol) was added. The resulting mixture was refluxed for 2 h and, after cooling, diluted with water (5 mL). The precipitate formed was isolated by filtration, washed with water, and dried to give **20** as a colorless powder. Yield 32 mg (31%), mp 203–204 °C; IR (KBr) 3412, 3304, 2242, 2228, 1615, 1598, 1548, 1491, 1473 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 6.95 (tt, 1H, CF_2CF_2H, $^2J_{H,F}$=51.9 Hz, $^3J_{H,F}$=4.5 Hz), 7.00 (td, 1H, H-5′, J=7.5, 1.0 Hz), 7.06 (dd, 1H, H-3′, J=8.3, 1.0 Hz), 7.41 (ddd, 1H, H-4′, J=8.3, 7.4, 1.7 Hz), 7.54 (dd, 1H, H-6′, J=7.7, 1.7 Hz), 10.62 (br s, 1H, OH), 14.47 (br s, 1H, NH). Anal. Calcd for $C_{12}H_7F_4N_3O$: C, 50.54; H, 2.47; N, 14.73. Found: C, 50.46; H, 2.23; N, 14.51.

*4.6.9. 5-(2′-Hydroxyphenyl)-1-phenyl-3-(1,1,2,2-tetrafluoroethyl)-1H-pyrazole-4-carbonitrile (**21**)*

A mixture of 3-cyanochromone **16c** (100 mg, 0.37 mmol) and phenylhydrazine (54 mg, 0.5 mmol) in methanol (3 mL) was heated to reflux for 3 h. After cooling, the resulting solution was diluted with water (5 mL) containing some drops of AcOH, the precipitate was filtered, washed with water, and dried to give **21** as a pale yellow powder. Yield 130 mg (98%), mp 192–193 °C; IR (KBr) 3336, 2248, 1612, 1594, 1542, 1505, 1489 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 6.88–6.92 (m, 2H, H-3′, H-5′), 7.03 (tt, 1H, CF_2CF_2H, $^2J_{H,F}$=51.7 Hz, $^3J_{H,F}$=4.3 Hz), 7.31–7.45 (m, 7H, H-4′, H-6′, Ph), 10.24 (s, 1H, OH). Anal. Calcd for $C_{18}H_{11}F_4N_3O$: C, 59.84; H, 3.07; N, 11.63. Found: C, 59.76; H, 2.95; N, 11.51.

*4.6.10. [5-Amino-3-(trifluoromethyl)isoxazol-4-yl](2′-hydroxy-5′-methylphenyl)methanone oxime (**22**)*

A mixture of $NH_2OH \cdot HCl$ (55 mg, 0.8 mmol) and AcONa (50 mg, 0.63 mmol) in methanol (3 mL) was heated to reflux for 5 min and then 3-cyanochromone **16b** (100 mg, 0.4 mmol) was added. The resulting mixture was refluxed for 2.5 h and, after cooling, diluted with water (10 mL). The precipitate formed was isolated by filtration, washed with water, dried, and recrystallized from toluene–hexane (3:1) to afford **22** as colorless crystals. Yield 56 mg (47%), mp 163–164 °C; IR (KBr) 3340, 1672, 1624, 1600, 1580, 1514, 1473 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.32 (s, 3H, Me), 5.12 (br s, 2H, NH_2), 5.20–6.80 (br s, 2H, 2OH), 6.94 (d, 1H, H-3′, J=8.4 Hz), 7.19 (br d, 1H, H-6′, J=2.0 Hz), 7.24 (ddq, 1H, H-4′, J=8.4, 2.3, 0.6 Hz); ^1H NMR (400 MHz, DMSO-d_6) δ 2.22 (s, 3H, Me), 5.89 (s, 2H, NH_2), 6.90 (d, 1H, H-3′, J=8.4 Hz), 7.20 (ddq, 1H, H-4′, J=8.4, 2.3, 0.6 Hz), 7.31 (br d, 1H, H-6′, J=2.0 Hz), 9.72 (s, 1H, OH), 10.20 (s, 1H, NOH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 19.9, 109.7, 112.5, 116.5, 119.6 (q, CF_3, $^1J_{C,F}$=271.8 Hz), 127.6, 130.4, 133.4, 142.1, 153.2 (q, C–CF_3, $^2J_{C,F}$=36.2 Hz), 153.7, 170.0; MS (EI): m/z (%) 301 $[M]^+$ (21), 284 $[M-NH_3]^+$ (67), 269 (100), 135 (54), 107 (21), 91 (19), 77 (55), 69 $[CF_3]^+$ (16), 51 (21). Anal. Calcd for $C_{12}H_{10}F_3N_3O_3$: C, 47.85; H, 3.35; N, 13.95. Found: C, 48.19; H, 3.41; N, 13.85.

*4.6.11. 2-Methyl-4-(trifluoromethyl)-5H-chromeno[4,3-d]-pyrimidin-5-one (**23a**) and 2-methyl-4-(trifluoromethyl)-5H-chromeno[4,3-d]pyrimidin-5-imine (**23b**)*

A mixture of acetamidine hydrochloride (60 mg, 0.63 mmol) and AcONa (50 mg, 0.63 mmol) in DMF (2 mL) was stirred at 100–110 °C for 5 min. After cooling, 3-cyanochromone **16a** (100 mg, 0.42 mmol) was added. The resulting mixture was refluxed for 15 min and diluted with water (6 mL). The precipitate formed was isolated by filtration, washed with water, dried, and recrystallized from methanol to afford a mixture of **23a** and **23b** as yellow crystals. Combined yield 27%, mp 160–163 °C; ^1H NMR (400 MHz, $CDCl_3$) **23a** (73%) δ 2.91 (s, 3H, Me), 7.16 (dd, 1H, H-7, J=8.3, 0.9 Hz), 7.29 (ddd, 1H, H-9, J=8.0, 7.3, 1.1 Hz), 7.59 (ddd, 1H, H-8, J=8.4, 7.3, 1.7 Hz), 8.50 (dd, 1H, H-10, J=8.0, 1.6 Hz); **23b** (27%) δ 2.95 (s, 3H, Me), 7.07 (ddd, 1H, H-9, J=8.2, 7.3, 1.2 Hz), 7.12 (dd, 1H, H-7, J=8.3, 1.2 Hz), 7.54 (ddd, 1H, H-8, J=8.4, 7.2, 1.6 Hz), 8.38 (dd, 1H, H-10, J=8.2, 1.6 Hz), 11.81 (br s, 1H, NH). Treatment of this mixture with aqueous AcOH at 85 °C for 3 h gave analytically pure coumarin **23a** as yellow needles, mp 182–183 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 2.92 (s, 3H, Me), 7.52 (ddd, 1H, H-9, J=8.0, 7.3, 1.1 Hz), 7.53 (dd, 1H, H-7, J=8.4, 1.1 Hz), 7.84 (ddd, 1H, H-8, J=8.4, 7.3, 1.7 Hz), 8.55 (dd, 1H, H-10, J=8.0, 1.7 Hz). Anal. Calcd for $C_{13}H_7F_3N_2O_2$: C, 55.72; H, 2.52; N, 10.00. Found: C, 55.85; H, 2.44; N, 10.12.

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