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One-pot three-component reaction of 3-(polyfluoroacyl)chromones with active methylene compounds and ammonium acetate: regioselective synthesis of novel R^F-containing nicotinic acid derivatives

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Abstract

Reactions of 3-(polyfluoroacyl)chromones with acetoacetamide and ethyl acetoacetate in the presence of ammonium acetate proceed at the C-2 atom of the chromone system with pyrone ring-opening and subsequent cyclization to 5-salicyloyl-2-methyl-6-(trifluoromethyl)nicotinamides, ethyl 5-salicyloyl-2-methyl-6-(trifluoromethyl)nicotinates, and ethyl 5-hydroxy-2-methyl-5-(polyfluoroalkyl)-5*H*-chromeno[4,3-*b*]pyridine-3-carboxylates. Similar reaction with β-aminocrotononitrile gave 5-hydroxy-2-methyl-5-(polyfluoroalkyl)-5*H*-chromeno[4,3-*b*]pyridine-3-carbonitriles.

Keywords: Three-component reactions; 3-(Polyfluoroacyl)chromones; Active methylene compounds; Ammonium acetate; Nicotinic acid derivatives

1. Introduction

The introduction of a polyfluoroacyl group into the 3-position of the chromone system changes crucially the reactivity of the pyrone ring with respect to nucleophiles and stipulates the broad synthetic potential of 3-(polyfluoroacyl)chromones. The diversity of properties of these compounds is due to the fact that, being actually highly reactive geminally activated push–pull alkenes with a good leaving group at the β-carbon atom, they acquire the ability to undergo additional transformations related to opening and recyclization of the γ-pyrone ring. Strangely enough, but these compounds have long remained out of sight of chemists engaged in organic synthesis, and their systematic study has started only in recent years. Nevertheless, it is already clear that 3-(polyfluoroacyl)chromones are valuable substrates for the synthesis of diverse fluorine-containing heterocycles with a potential biological activity.[1] The reactions of these compounds with such dinucleophiles as hydrazines and hydroxylamine 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. Along with this route, the initial attack can proceed at the 3-R^FCO group as well (1,2-addition), which does not exclude the variant of recyclization due to the intramolecular Michael reaction and the subsequent ring-opening with cleavage of the O(1)–C(2) bond.[2]

As a continuation of our studies on the synthetic potential of 3-(polyfluoroacyl)chromones, and owing to the increasing importance of fluorine-containing heterocycles in biology, pharmacology, and industrial applications,[3] we decided to investigate their reactions with acetoacetamide and acetoacetic ester in the presence of ammonium acetate, as well as with ethyl β-aminocrotonate and β-aminocrotononitrile in order to develop a simple synthesis of novel R^F-containing nicotinic acid derivatives. It has been shown previously that 3-formylchromone **1** readily reacts with active methylene compounds and ammonia to give pyridine derivatives **2**–**4**, depending on the

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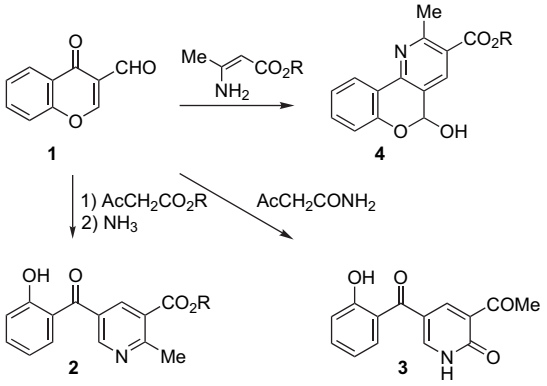
reaction conditions and the nature of dinucleophiles (Scheme 1).[4] The formation of compounds **2** and **3** can proceed via both the 1,4- and 1,2-addition of the central carbon atom of the active methylene molecule due to chemical equivalence of the CHO group and C-2 atom of **1**. However, chromenopyridine **4** certainly is the product of the primary 1,4-addition followed by the pyrone ring-opening, attack of the NH_2 group to the carbonyl bound with the aromatic cycle, and ring-closure involving the phenolic hydroxyl and CHO group.



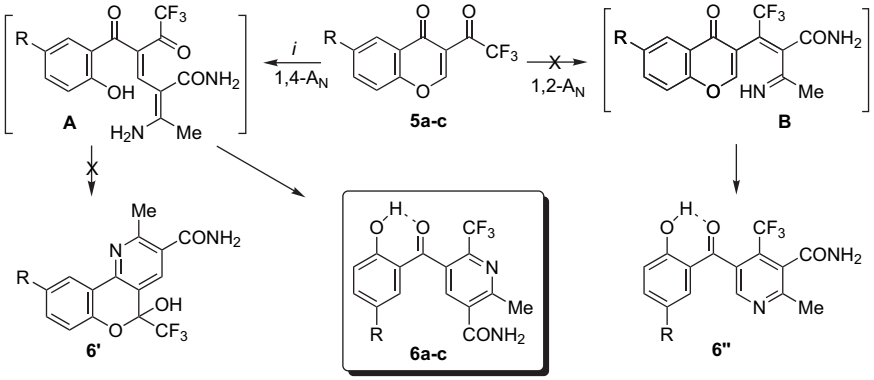
Scheme 1.

On the other hand, remarkable progress has been made in the development of new and efficient methods for synthesis of polyfluoroalkylated pyridine derivatives using fluorinated building blocks. 2,6-Diaryl-4-(trifluoromethyl)pyridines have recently been synthesized by the reaction of enamines, prepared from substituted acetophenones and morpholine, with trifluoromethylated β-diketones in the presence of ammonium acetate.[5a] The condensation of CF_3-containing α,β-unsaturated ketones and β-diketones with primary enamines, such as β-aminocrotononitrile and ethyl β-aminocrotonates, affords 2- and 4-(trifluoromethyl)pyridines.[5b–f] These compounds were also obtained from the reaction of trifluoromethylated α,β-unsaturated ketones and β-diketones with *N*-silyl-1-azaallyl anions,[5g] by Hantzsch's dihydropyridine synthesis[5h,i] and Suzuki cross-coupling.[5j]

2. Results and discussion

Herein, we wish to report the successful regioselective synthesis of novel R^F-containing nicotinic acid derivatives from 3-(polyfluoroacyl)chromones **5** and enamines arising from active methylene compounds. We have reasoned that when chromones **5** were coupled with these 1,3-C,N-dinucleophiles, the similar electrophilic character of the C-2 atom and the carbonyl carbon of 3-polyfluoroacyl group would lead to a mixture of regioisomeric products. However, when chromones **5a–c** were treated in refluxing ethanol with acetoacetamide in the presence of ammonium acetate, a smooth reaction took place and 2-methyl-5-salicyloyl-6-(trifluoromethyl)nicotinamides **6a–c** were obtained in moderate yields (Scheme 2). Compounds **6a–c** are precipitated from the reaction solution and analytically pure products can be isolated by simple filtration. In the light of the present interest in fluoroheteroaromatics as pharmaceutical intermediates,[3] this novel entry to fluorinated nicotinamides is noteworthy.

The first step of the reaction consists apparently of an attack at the C-2 atom of chromones by the internal carbon of β-aminocrotonamide (in general, this atom is more nucleophilic than the primary amino group in acidic conditions) with concomitant opening of the pyrone ring (1,4-addition, intermediate **A**), and finally, the intramolecular attack at the CF_3CO group by the amino group leads to 6-CF_3-pyridines **6a–c**. The driving force of the dehydration is probably due to the formation of an



Reaction conditions (i): $AcCH_2CONH_2$, $AcONH_4$, EtOH

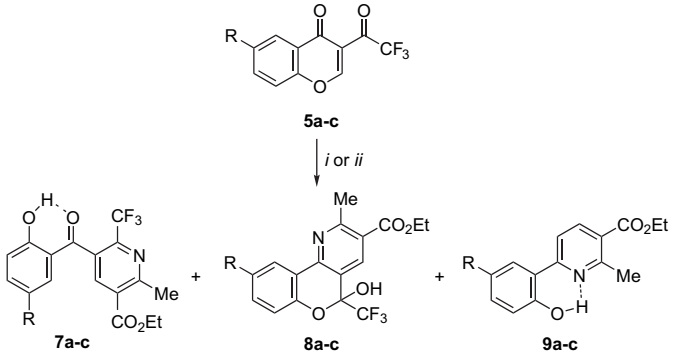
Chromone	R	Product	Yield (%)	Mp (°C)
5a	H	**6a**	46	252–253
5b	Me	**6b**	50	242–243
5c	Cl	**6c**	48	228–229

Scheme 2.

aromatic pyridine derivative. The alternative cyclization of **A** involving the amino group and the carbonyl carbon atom connected to the benzene ring to give chromeno[4,3-*b*]pyridines **6′** does not occur. Note that for the initial attack of the CF_3CO group by the internal atom of β-aminocrotonamide (1,2-addition) the reaction through the ring-closure/ring-opening sequence would result in isomeric 4-CF_3-pyridines **6″**.

All signals in the ^1H and ^{13}C NMR spectra of compound **6a** were assigned on the basis of 2D HSQC and HMBC experiments. For choosing between structures **6** and **6″**, the former one was decisively favored by the fact that the H-4 proton is bound due to the $^3J_{C,H}$ coupling constants with the carbon atoms C-2, C-6, CO, and NCO (in the case of **6″**, the latter constant could not appear). In addition, the C-4 atom has the upfield chemical shift (134.85 ppm), which is not characteristic of atoms directly bound to the pyridine nitrogen atom. Thus, the regiochemistry was determined and higher reactivity of a CF_3CO than ArCO of intermediate **A** toward the amino group was shown.

It has been reported previously that pyridine **2** (R=Me), prepared by condensation of 3-formylchromone **1** with methyl acetoacetate followed by treatment with ammonia, is isomeric to pyridine **4** from the reaction of **1** with methyl β-aminocrotonate.[4a] However, in our case, the reactions of chromones **5a–c** with both ethyl acetoacetate in the presence of ammonium acetate and ethyl β-aminocrotonate gave the same result. In all cases, mixtures of approximately equal amounts of compounds **7a–c** and **8a–c** were obtained (Scheme 3). The products arising from chromones **5a**,**b** were separated by recrystallization from methanol or hexane/ether, and the isolated yield of **7a**,**b** and **8b** was 12–20%. The structures of products **7b** and **8b** were established by their elemental and spectral analyses, including 2D HSQC and HMBC experiments. Note that isomers **7b** and **8b** can easily be distinguished by the ^{19}F NMR spectra in which the singlet of the CF_3 group is observed at 99.65 and 78.84 ppm (DMSO-d_6, HFB), respectively. Besides compounds **7** and **8**, a small amount of pyridines **9** has also been detected by ^1H NMR spectroscopy, although we have been unable to isolate them in pure form. The ^1H NMR spectra of compounds **9a–c** revealed two doublets at δ 7.76–7.81 ppm ($CDCl_3$) or 8.15–8.17 ppm (DMSO-d_6) due to H-5 and 8.35–8.40 ppm



Reaction conditions (i): $AcCH_2CO_2Et$, $AcONH_4$, EtOH;
(ii) $MeC(NH_2)C{=}CHCO_2Et$, AcOH, EtOH;
R = H (**a**), Me (**b**), Cl (**c**)

Scheme 3.

($CDCl_3$, DMSO-d_6) due to H-4 with a coupling constant value ^3J=8.5 Hz. Such coupling value is characteristic for pyridine protons H-3 and H-4 and much higher than that for H-2 and H-3 (4–6 Hz).[6] These pyridines are likely the result of the in situ detrifluoroacetylation of chromenopyridines **8** (Scheme 3). The mechanism probably follows a course similar to that described in Scheme 2. Thus, ethyl β-aminocrotonate in the reaction with **5a–c** turned out to be less selective reactant, whose amino group attacks both carbonyls in intermediate **A** with equal success.

As expected, regioselectivity of the nucleophilic attack by the NH_2 group of intermediate **A** on the two carbonyl carbon atoms will depend on the electronic and steric effects of the R^F group. In fact, the reaction of chromones **5d–h** with acetoacetic ester under the same reaction conditions afforded chromeno[4,3-*b*]-pyridine-3-carboxylates **8d–h** in 26–69% isolated yields. In this reaction, the attack of the NH_2 group is mainly directed to the carbonyl at the aromatic ring, due to which the R^FCO group remains free and can participate in the formation of cyclic semiketal form **8**. In the case of **5f–h**, the improved regioselectivity is probably due to the steric bulk of the $H(CF_2)_2$ group and the lower electrophilicity of the carbonyl carbon atom connected to this group (Scheme 4).

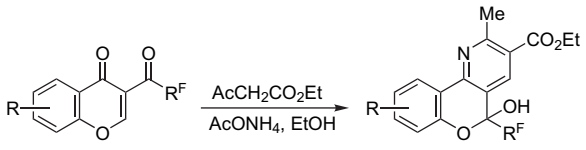
Similarly, the reaction of chromones **5c–g** with β-aminocrotononitrile in refluxing ethanol in the presence of acetic acid gave chromenopyridines **10c–g**. Only one regioisomer has been obtained in this two-component condensation, albeit in only 23–42% yields. As it was expected, the lowest yield of the products was obtained for CF_3-substituted chromones **5c**,**d**, whose reaction is less unambiguous (Scheme 5). In the cases of compounds **8f**,**g** and **10f**,**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 6.78–6.82 ppm) is split into a triplet of doublets of doublets with $^2J_{H,F}$=51.6–51.8 Hz and $^3J_{H,F}$=7.4–7.9, 5.3–5.6 Hz instead of the usual triplet of triplets.

Finally, we have found that dimedone enamine arising from dimedone and ammonium acetate in refluxing ethanol reacted with chromones **5a**,**b**,**e–g** and gave 2-(2-hydroxyaryl)-7,7-dimethyl-7,8-dihydroquinolin-5(6*H*)-ones **11a**,**b** in low yields (22–25%). The reaction includes the nucleophilic 1,4-addition of the internal carbon atom with concomitant opening of the pyrone ring and subsequent intramolecular cyclization with the participation of the NH_2 and ArCO groups followed by depolyfluoroacylation (Scheme 6).

Note that unsubstituted chromone under the same reaction conditions gave compound **11a** in only 7% yield. A characteristic feature of the ^1H NMR spectra of **11a**,**b** is the appearance of two AB doublets (J=8.6 Hz) at δ 8.2 and 8.3 ppm for the pyridine H-3 and H-4 protons and a singlet at δ 13.7–14.0 ppm corresponding to the OH proton resonance.

3. Conclusion

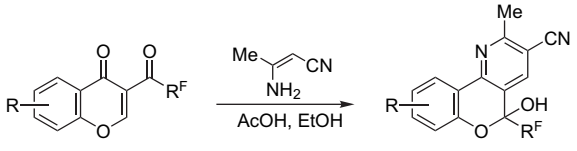
In conclusion, we have shown that 3-(polyfluoroacyl)chromones, readily available from the condensation products of 2-hydroxyacetophenones with R^FCO_2Et and diethoxymethyl



5d-h **8d-h**

Chromone	R	R^F	Product	Yield (%)	Mp (°C)
5d	7-MeO	CF_3	**8d**	31	213–214
5e	H	CF_2H	**8e**	26	184–185
5f	H	$(CF_2)_2H$	**8f**	69	180–181
5g	6-Me	$(CF_2)_2H$	**8g**	34	218–219
5h	7-MeO	$(CF_2)_2H$	**8h**	50	208–209

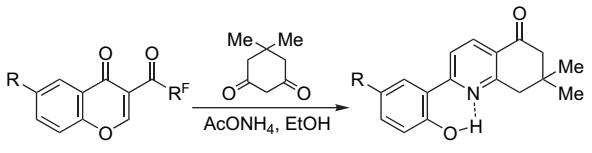
Scheme 4.



5c-g **10c-g**

Chromone	R	R^F	Product	Yield (%)	Mp (°C)
5c	6-Cl	CF_3	**10c**	23	192–194
5d	7-MeO	CF_3	**10d**	24	236–238
5e	H	CF_2H	**10e**	41	212–214
5f	H	$(CF_2)_2H$	**10f**	42	193–194
5g	6-Me	$(CF_2)_2H$	**10g**	36	220–222

Scheme 5.



5a,b,e-g R = H (**11a**), Me (**11b**)

Scheme 6.

acetate,[1] reacted with active methylene compounds and ammonium acetate giving either densely substituted pyridines or chromeno[4,3-*b*]pyridines, depending on the nature of 1,3-C,N-dinucleophile and the length of the polyfluoroalkyl group. By proper choice of these parameters the R^F-containing pyridines could be selectively obtained in moderate yields. In addition, the method appears to be useful and convenient in terms of the ready accessibility of the starting materials, cheap reagents, and operational simplicity.

4. Experimental

4.1. General

^1H (400 MHz), ^{13}C (100 MHz), and ^{19}F (376 MHz) NMR spectra were recorded on a Bruker DRX-400 spectrometer in DMSO-d_6 with TMS and C_6F_6 as internal standards, respectively. Assignment of chemical shifts was based on standard 2D NMR techniques ($^1H-^{13}C$ HSQC and HMBC). IR spectra were recorded on a 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 as per standard procedures. The starting chromones **5a–h** were prepared according to described procedure.[1]

4.2. General procedure for pyridines 6a–c

A mixture of chromone **5** (1.0 mmol), acetoacetamide (250 mg, 2.5 mmol), and ammonium acetate (1.0 g, 13.0 mmol) in ethanol (5 mL) was refluxed for 4 h. Then the solvent was evaporated at heating to half of its initial volume and then cooled. The precipitate formed was filtered and washed with aqueous ethanol (1:1) to give pyridines **6** as colorless crystals.

4.2.1. 5-Salicyloyl-2-methyl-6-(trifluoromethyl)nicotinamide (6a)

Yield 46%, mp 252–253 °C; IR (KBr) 3399, 3316, 3171, 1696, 1623, 1607, 1576, 1488 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 2.67 (s, 3H, Me), 6.95–7.00 (m, 2H, H-3′, H-5′), 7.54–7.60 (m, 2H, H-4′, H-6′), 7.82 (br s, 1H, NH), 7.98 (s, 1H, H-4), 8.12 (br s, 1H, NH), 10.83 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 22.5 (Me), 117.7 (C-3′), 119.5 (C-5′), 121.1 (q, CF_3, $^1J_{C,F}$=275.4 Hz), 121.4 (C-1′), 131.79 (C-4′), 133.1 (q, C-5, $^3J_{C,F}$=1.2 Hz), 134.6 (C-3), 134.9 (C-4), 136.8 (C-6′), 141.4 (q, C-6, $^2J_{C,F}$=33.8 Hz), 156.5 (C-2), 160.0 (C-2′), 167.8 (NCO), 194.5 (CO). Anal. Calcd for $C_{15}H_{11}F_3N_2O_3$: C, 55.56; H, 3.42; N, 8.64. Found: C, 55.40; H, 3.42; N, 8.40.

4.2.2. 5-(2′-Hydroxy-5′-methylbenzoyl)-2-methyl-6-(trifluoromethyl)nicotinamide (6b)

Yield 50%, mp 242–243 °C; IR (KBr) 3380, 3317, 3180, 1699, 1630, 1598, 1586, 1482 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 2.23 (s, 3H, Me), 2.67 (s, 3H, Me), 6.87 (d, 1H, H-3′, ^4J=8.4 Hz), 7.34 (br d, 1H, H-6′, ^3J=1.6 Hz), 7.39 (dd, 1H, H-4′, ^4J=8.4 Hz, ^3J=2.2 Hz), 7.81 (s, 1H, NH), 7.94 (s, 1H, H-6), 8.10 (s, 1H, NH), 10.61 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 19.8, 22.5, 117.6, 121.0, 121.1 (q, CF_3, 275.3 Hz), 128.3, 131.2, 133.2, 134.5, 134.8, 137.8, 141.4 (q, C–CF_3, 33.7 Hz), 156.4, 158.0, 167.8, 194.5. Anal. Calcd for $C_{16}H_{13}F_3N_2O_3$: C, 56.81; H, 3.87; N, 8.28. Found: C, 56.73; H, 3.67; N, 8.22.

4.2.3. 5-(5′-Chloro-2′-hydroxybenzoyl)-2-methyl-6-(trifluoromethyl)nicotinamide (6c)

Yield 48%, mp 228–229 °C; IR (KBr) 3386, 3318, 3177, 1698, 1624, 1602, 1571, 1467 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 2.67 (s, 3H, Me), 6.95 (d, 1H, H-3′, ^4J=8.8 Hz), 7.58 (dd, 1H, H-4′, ^4J=8.8 Hz, ^3J=2.8 Hz), 7.62 (d, 1H, H-6′, ^3J=2.8 Hz), 7.81 (s, 1H, NH), 7.96 (s, 1H, H-4), 8.09 (s, 1H, NH), 10.86 (s, 1H, OH); ^{19}F NMR (376 MHz, DMSO-d_6, HFB) δ 99.89 (s, CF_3). Anal. Calcd for $C_{15}H_{10}ClF_3N_2O_3$: C, 50.23; H, 2.81; N, 7.81. Found: C, 50.16; H, 2.68; N, 8.10.

4.3. General procedures for pyridines 7–9

Procedure *A*. A mixture of chromone **5** (1.0 mmol), ethyl acetoacetate (320 mg, 2.5 mmol), and ammonium acetate (1.0 g, 13.0 mmol) in ethanol (5 mL) was refluxed for 4 h. The resultant reaction mixture was cooled and diluted with water. The precipitate that formed was filtered and washed with cooled aqueous ethanol (1:1) to give a mixture of **7–9**.

Procedure *B*. A solution of chromone **5** (1 mmol), acetic acid (240 mg, 4.0 mmol), and ethyl β-aminocrotonate (260 mg, 2.0 mmol) in ethanol (5 mL) was refluxed for 0.5–4 h. After the removal of solvent under reduced pressure, the residue was purified by recrystallization from benzene, toluene or methanol to give a mixture of **7–9**.

4.3.1. Ethyl 5-salicyloyl-2-methyl-6-(trifluoromethyl)-nicotinate (7a)

This compound was prepared according to procedure *A* from a mixture of composition **7a/8a/9**=35:50:15 by recrystallization from hexane/ether (10:1). Yield 18%, mp 103–104 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 1.40 (t, 3H, Me, J=7.1 Hz), 2.98 (s, 3H, Me), 4.42 (q, 2H, CH_2, J=7.1 Hz), 6.86 (ddd, 1H, H-5′, ^3J=8.0, 7.2 Hz, ^4J=1.0 Hz), 7.09 (dd, 1H, H-6′, ^3J=8.0 Hz, ^4J=1.6 Hz), 7.10 (dd, 1H, H-3′, ^3J=8.5 Hz, ^4J=1.0 Hz), 7.56 (ddd, 1H, H-4′, ^3J=8.5, 7.2 Hz, ^4J=1.6 Hz), 8.25 (s, 1H, H-4), 11.65 (s, 1H, OH); ^{19}F NMR (376 MHz, $CDCl_3$, HFB) δ 97.92 (s, CF_3). Anal. Calcd for $C_{17}H_{14}F_3NO_4$: C, 57.79; H, 3.99; N, 3.96. Found: C, 57.71; H, 4.06; N, 3.90.

4.3.2. Ethyl 5-hydroxy-2-methyl-5-(trifluoromethyl)-5H-chromeno[4,3-b]pyridine-3-carboxylate (8a) and ethyl 6-(2′-hydroxyphenyl)-2-methylnicotinate (9a)

These compounds were not obtained in pure form. ^1H NMR (400 MHz, $CDCl_3$) Compound **8a**: δ 1.41 (t, 3H, Me, J=7.1 Hz), 2.90 (s, 3H, Me), 4.38 (q, 2H, CH_2, J=7.1 Hz), 5.0–5.2 (br s, 1H, OH), 7.01 (dd, 1H, H-7, ^3J=8.2 Hz, ^4J=0.9 Hz), 7.10 (m, 1H, H-9), 7.35 (ddd, 1H, H-8, ^3J=8.2, 7.4 Hz, ^4J=1.7 Hz), 8.25 (dd, 1H, H-10, ^3J=7.8 Hz, ^4J=1.7 Hz), 8.32 (s, 1H, H-4); ^1H NMR (400 MHz, DMSO-d_6) Compound **9a**: δ 1.33 (t, 3H, Me, J=7.1 Hz), 2.82 (s, 3H, Me), 4.31–4.40 (m, 2H, OCH_2), 6.93–7.00 (m, 2H, H-3′, H-5′), 7.37 (ddd, 1H, H-4′, ^3J=8.5, 7.0 Hz, ^4J=1.6 Hz), 8.06 (dd, 1H, H-6′, ^3J=8.2 Hz, ^4J=1.6 Hz), 8.17 (d, 1H, H-5, ^3J=8.5 Hz), 8.36 (d, 1H, H-4, ^3J=8.5 Hz), 14.08 (s, 1H, OH).

4.3.3. Ethyl 5-(2′-hydroxy-5′-methylbenzoyl)-2-methyl-6-(trifluoromethyl)nicotinate (7b)

This compound was prepared according to procedure *B* from a mixture of composition **7b/8b**=76:24 by recrystallization from methanol. Yield 20%, mp 140–142 °C; IR (KBr) 1732, 1638, 1620, 1592, 1555, 1487 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.32 (t, 3H, Me, J=7.1 Hz), 2.24 (s, 3H, Me), 2.84 (s, 3H, Me), 4.35 (q, 2H, CH_2, J=7.1 Hz), 6.87 (d, 1H, H-3′, ^3J=8.4 Hz), 7.38 (dd, 1H, H-4′, ^3J=8.5 Hz, ^4J=2.3 Hz), 7.43 (d, 1H, H-6′, ^4J=2.2 Hz), 8.32 (s, 1H, H-4), 10.57 (s, 1H, OH); ^1H NMR (400 MHz, $CDCl_3$) δ 1.41 (t, 3H, Me, J=7.1 Hz), 2.20 (s, 3H, Me), 2.99 (s, 3H, Me), 4.43 (q, 2H, CH_2, J=7.1 Hz), 6.82 (br d, 1H, H-6′, ^4J=1.5 Hz), 7.00 (d, 1H, H-3′, ^3J=8.5 Hz), 7.37 (dd, 1H, H-4′, ^3J=8.5 Hz, ^4J=2.0 Hz), 8.24 (s, 1H, H-4), 11.50 (s, 1H, OH); ^{19}F NMR (376 MHz, DMSO-d_6, HFB) δ 99.65 (s, CF_3); ^{19}F NMR

(376 MHz, $CDCl_3$, HFB) δ 97.92 (s, CF_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 13.8 (CH_2*Me*), 19.7 (Ar*Me*), 23.9 (Py*Me*), 61.8 (OCH_2), 117.6 (C-3′), 120.9 (q, CF_3, $^1J_{C,F}$=275.7 Hz), 121.2 (C-1′), 124.4 (C-3), 128.3 (C-5′), 131.0 (C-6′), 133.9 (q, C-5, $^3J_{C,F}$=1.2 Hz), 137.7 (C-4′), 137.9 (C-4), 143.1 (q, C-6, $^2J_{C,F}$=34.1 Hz), 157.8 (C-2′), 159.0 (C-2), 164.6 (COO), 193.5 (CO); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2 (CH_2*Me*), 20.3 (Ar*Me*), 24.7 (Py*Me*), 62.2 (OCH_2), 118.5 (C-3′), 119.0 (C-1′), 120.7 (q, CF_3, $^1J_{C,F}$=276.1 Hz), 127.8 (C-3), 128.7 (C-5′), 130.1 (C-6′), 132.2 (C-5), 138.8 (C-4′), 139.0 (C-4), 145.3 (q, C-6, $^2J_{C,F}$=35.0 Hz), 161.2 (C-2′), 161.4 (C-2), 164.7 (COO), 197.9 (CO). Anal. Calcd for $C_{18}H_{16}F_3NO_4$: C, 58.86; H, 4.39; N, 3.81. Found: C, 58.94; H, 4.12; N, 3.70.

*4.3.4. Ethyl 5-hydroxy-2,9-dimethyl-5-(trifluoromethyl)-5H-chromeno[4,3-b]pyridine-3-carboxylate (**8b**)*

This compound was prepared according to procedure *A* from a mixture of composition **7b/8b/9b**=55:35:10 by recrystallization from hexane/ether (1:1). Yield 12%, mp 184–185 °C; IR (KBr) 1729, 1638, 1621, 1589, 1560 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.36 (t, 3H, Me, *J*=7.1 Hz), 2.36 (s, 3H, Me), 2.86 (s, 3H, Me), 4.38 (br q, 2H, CH_2, *J*=7.0 Hz), 7.05 (d, 1H, H-7, ^3J=8.3 Hz), 7.31 (dd, 1H, H-8, ^3J=8.4 Hz, ^4J=2.0 Hz), 8.09 (d, 1H, H-10, ^4J=2.3 Hz), 8.32 (s, 1H, H-4), 9.48 (s, 1H, OH); ^1H NMR (400 MHz, $CDCl_3$) δ 1.42 (t, 3H, Me, *J*=7.1 Hz), 2.35 (s, 3H, Me), 2.90 (s, 3H, Me), 4.38 (q, 2H, CH_2, *J*=7.1 Hz), 4.8–5.2 (br s, 1H, OH), 6.92 (d, 1H, H-7, ^3J=8.3 Hz), 7.16 (dd, 1H, H-8, ^3J=8.3 Hz, ^4J=1.9 Hz), 8.04 (br d, 1H, H-10, ^4J=1.7 Hz), 8.33 (s, 1H, H-4); ^{19}F NMR (376 MHz, DMSO-d_6, HFB) δ 78.84 (s, CF_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 14.0 (CH_2*Me*), 20.2 (Ar*Me*), 24.7 (Py*Me*), 61.3 (OCH_2), 95.7 (q, C-5, $^2J_{C,F}$=32.5 Hz), 116.5 (C-7), 118.1 (C-10a), 119.9 (C-3), 122.38 (q, CF_3, $^1J_{C,F}$=289.0 Hz), 124.7 (C-10), 128.2 (q, C-4a, $^3J_{C,F}$=1.2 Hz), 131.9 (C-9), 133.8 (C-8), 137.1 (q, C-4, $^4J_{C,F}$=1.2 Hz), 148.7 (C-10b), 150.8 (C-6a), 161.3 (C-2), 165.1 (COO). Anal. Calcd for $C_{18}H_{16}F_3NO_4$: C, 58.86; H, 4.39; N, 3.81. Found: C, 58.52; H, 4.38; N, 3.89.

*4.3.5. Ethyl 6-(2′-hydroxy-5′-methylphenyl)-2-methylnicotinate (**9b**)*

This compound was not obtained in pure form. ^1H NMR (400 MHz, DMSO-d_6) δ 1.35 (t, 3H, Me, *J*=7.1 Hz), 2.31 (s, 3H, Me), 2.81 (s, 3H, Me), 4.35–4.40 (q, 2H, CH_2, *J*=7.1 Hz), 6.86 (d, 1H, H-3′, ^3J=8.4 Hz), 7.18 (dd, 1H, H-4′, ^3J=8.5 Hz, ^4J=2.0 Hz), 7.86 (d, 1H, H-6′, ^4J=2.0 Hz), 8.15 (d, 1H, H-5, ^3J=8.5 Hz), 8.35 (d, 1H, H-4, ^4J=8.5 Hz), 13.84 (s, 1H, OH); ^1H NMR (400 MHz, $CDCl_3$) δ 1.43 (t, 3H, Me, *J*=7.1 Hz), 2.35 (s, 3H, Me), 2.91 (s, 3H, Me), 4.41 (q, 2H, CH_2, *J*=7.1 Hz), 6.97 (d, 1H, H-3′, ^3J=8.5 Hz), 7.17 (br d, 1H, H-4′, ^3J=8.5 Hz), 7.60 (br s, 1H, H-6′), 7.81 (d, 1H, H-5, ^3J=8.5 Hz), 8.37 (d, 1H, H-4, ^3J=8.5 Hz).

*4.3.6. Ethyl 5-(5′-chloro-2′-hydroxybenzoyl)-2-methyl-6-(trifluoromethyl)nicotinate (**7c**), ethyl 9-chloro-5-hydroxy-2-methyl-5-(trifluoromethyl)-5H-chromeno[4,3-b]pyridine-3-carboxylate (**8c**), and ethyl 5-(5′-chloro-2′-hydroxybenzoyl)-2-methyl-4-(trifluoromethyl)nicotinate (**9c**)*

A mixture of composition **7c/8c/9c**=4:5:1 was obtained according to procedures *A* and *B*. ^1H NMR (400 MHz, $CDCl_3$) Compound **7c**: δ 1.43 (t, 3H, Me, *J*=7.1 Hz), 2.99 (s, 3H, Me), 4.44 (q, 2H, CH_2, *J*=7.1 Hz), 7.01 (d, 1H, H-3′, ^3J=8.8 Hz), 7.03 (d, 1H, H-6′, ^3J=2.6 Hz), 7.51 (dd, 1H, H-4′, ^3J=8.7 Hz, ^4J=2.6 Hz), 8.24 (s, 1H, H-4), 11.57 (s, 1H, OH); Compound **8c**: δ 1.42 (t, 3H, Me, *J*=7.1 Hz), 2.92 (s, 3H, Me), 4.41 (q, 2H, CH_2, *J*=7.1 Hz), 4.6–5.4 (br s, 1H, OH), 7.07 (d, 1H, H-7, ^3J=8.9 Hz), 7.34 (dd, 1H, H-8, ^3J=8.8 Hz, ^4J=2.6 Hz), 8.37 (d, 1H, H-10, ^4J=2.6 Hz), 8.45 (s, 1H, H-4); Compound **9c**: δ 1.43 (t, 3H, Me, *J*=7.1 Hz), 2.91 (s, 3H, Me), 4.42 (q, 2H, CH_2, *J*=7.1 Hz), 7.00 (d, 1H, H-3′, ^3J=8.9 Hz), 7.27 (dd, 1H, H-4′, ^3J=8.9 Hz, ^4J=2.5 Hz), 7.75 (d, 1H, H-6′, ^4J=2.5 Hz), 7.76 (d, 1H, H-5, ^3J=8.5 Hz), 8.40 (d, 1H, H-4, ^3J=8.5 Hz).

*4.3.7. Ethyl 5-hydroxy-8-methoxy-2-methyl-5-(trifluoromethyl)-5H-chromeno[4,3-b]pyridine-3-carboxylate (**8d**)*

This compound was prepared according to procedure *A*. Yield 31%, mp 213–214 °C; IR (KBr) 1723, 1653, 1620, 1588, 1559, 1512 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.34 (t, 3H, Me, *J*=7.1 Hz), 2.83 (s, 3H, Me), 3.84 (s, 3H, MeO), 4.34 (dq, 1H, C*H*H, *J*=10.8, 7.1 Hz), 4.37 (dq, 1H, CH*H*, *J*=10.8, 7.1 Hz), 6.71 (d, 1H, H-7, ^4J=2.4 Hz), 6.79 (dd, 1H, H-9, ^3J=8.8 Hz, ^4J=2.4 Hz), 8.17 (d, 1H, H-10, ^3J=8.8 Hz), 8.26 (s, 1H, H-4), 9.53 (s, 1H, OH). Anal. Calcd for $C_{18}H_{16}F_3NO_5 \cdot 0.25H_2O$: C, 55.75; H, 4.29; N, 3.61. Found: C, 55.57; H, 4.15; N, 3.58.

*4.3.8. Ethyl 5-(difluoromethyl)-5-hydroxy-2-methyl-5H-chromeno[4,3-b]pyridine-3-carboxylate (**8e**)*

This compound was prepared according to procedure *B*. Yield 26%, mp 184–185 °C; IR (KBr) 3094, 1729, 1612, 1602, 1588, 1557, 1490 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.35 (t, 3H, Me, *J*=7.1 Hz), 2.84 (s, 3H, Me), 4.35 (dq, 1H, C*H*H, *J*=10.8, 7.1 Hz), 4.38 (dq, 1H, CH*H*, *J*=10.8, 7.1 Hz), 6.31 (t, 1H, CF_2H, $^2J_{H,F}$=54.4 Hz), 7.08 (dd, 1H, H-7, ^3J=8.2 Hz, ^4J=0.9 Hz), 7.17 (td, 1H, H-9, ^3J=7.7 Hz, ^4J=1.0 Hz), 7.47 (ddd, 1H, H-8, ^3J=8.3, 7.3 Hz, ^4J=1.7 Hz), 8.26 (dd, 1H, H-10, ^3J=7.8 Hz, ^4J=1.7 Hz), 8.29 (s, 1H, H-4), 8.78 (br s, 1H, OH). Anal. Calcd for $C_{17}H_{15}F_2NO_4$: C, 60.89; H, 4.51; N, 4.18. Found: C, 60.58; H, 4.32; N, 3.98.

*4.4. General procedure for pyridines **8f–h***

A mixture of chromone **5f–h** (1 mmol), ethyl acetoacetate (320 mg, 2.5 mmol), and ammonium acetate (1.0 g, 13.0 mmol) in ethanol (5 mL) was refluxed for 4 h. Then the solvent was evaporated to half of its initial volume and then cooled. The precipitate formed was filtered and washed with cooled aqueous ethanol (1:1) to give pyridines **8f–h** as colorless crystals.

*4.4.1. Ethyl 5-hydroxy-2-methyl-5-(1,1,2,2-tetrafluoroethyl)-5H-chromeno[4,3-b]pyridine-3-carboxylate (**8f**)*

Yield 69%, mp 180–181 °C; IR (KBr) 3430, 1730, 1588, 1558 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.36 (t, 3H,

Me, J=7.1 Hz), 2.86 (s, 3H, Me), 4.37 (br q, 2H, CH_2, J=7.0 Hz), 6.82 (tdd, 1H, CF_2CF_2H, $^2J_{H,F}$=51.8 Hz, $^3J_{H,F}$=7.4, 5.3 Hz), 7.09 (d, 1H, H-7, ^3J=8.1 Hz), 7.19 (t, 1H, H-9, ^3J=7.5 Hz), 7.49 (t, 1H, H-8, ^3J=7.6 Hz), 8.26 (d, 1H, H-10, ^3J=7.6 Hz), 8.30 (s, 1H, H-4), 9.45 (s, 1H, OH). Anal. Calcd for $C_{18}H_{15}F_4NO_4$: C, 56.11; H, 3.92; N, 3.64. Found: C, 56.23; H, 3.88; N, 3.71.

*4.4.2. Ethyl 5-hydroxy-2,9-dimethyl-5-(1,1,2,2-tetrafluoroethyl)-5H-chromeno[4,3-b]pyridine-3-carboxylate (**8g**)*

Yield 34%, mp 218–219 °C; IR (KBr) 3438, 1728, 1590, 1561 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.35 (t, 3H, Me, J=7.1 Hz), 2.35 (s, 3H, Me), 2.85 (s, 3H, Me), 4.35 (dq, 1H, C*H*H, J=10.9, 7.1 Hz), 4.38 (dq, 1H, CH*H*, J=10.9, 7.1 Hz), 6.80 (tdd, 1H, CF_2CF_2H, $^2J_{H,F}$=51.8 Hz, $^3J_{H,F}$=7.9, 5.2 Hz), 6.98 (d, 1H, H-7, ^3J=8.4 Hz), 7.29 (dd, 1H, H-8, ^3J=8.4 Hz, ^4J=2.0 Hz), 8.06 (d, 1H, H-10, ^4J=2.0 Hz), 8.29 (d, 1H, H-4, J=1.5 Hz), 9.38 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 14.0 (CH_2*Me*), 20.3 (Ar*Me*), 24.8 (Py*Me*), 61.3 (OCH_2), 97.3 (dd, C-5, $^2J_{C,F}$=29.8, 26.0 Hz), 108.6 (tt, CF_2H, $^1J_{C,F}$=250.3, $^2J_{C,F}$=29.0 Hz), 113.6 (tt, CF_2, $^1J_{C,F}$=260.6, $^2J_{C,F}$=22.8 Hz), 116.5 (C-7), 118.5 (C-10a), 120.4 (C-4a), 124.1 (C-3), 124.6 (C-10), 131.7 (C-9), 133.6 (C-8), 137.8 (d, C-4, $^4J_{C,F}$=3.1 Hz), 149.1 (C-10b), 151.1 (C-6a), 161.0 (C-2), 165.2 (COO). Anal. Calcd for $C_{19}H_{17}F_4NO_4$: C, 57.15; H, 4.29; N, 3.51. Found: C, 57.17; H, 4.26; N, 3.83.

*4.4.3. Ethyl 5-hydroxy-8-methoxy-2-methyl-5-(1,1,2,2-tetrafluoroethyl)-5H-chromeno[4,3-b]pyridine-3-carboxylate (**8h**)*

Yield 50%, mp 208–209 °C; IR (KBr) 3445, 1718, 1622, 1586, 1514 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.34 (t, 3H, Me, J=7.1 Hz), 2.83 (s, 3H, Me), 3.83 (s, 3H, OMe), 4.34 (dq, 1H, C*H*H, J=11.0, 7.1 Hz), 4.37 (dq, 1H, CH*H*, J=11.0, 7.1 Hz), 6.64 (d, 1H, H-7, ^4J=2.4 Hz), 6.77 (dd, 1H, H-9, ^3J=8.7 Hz, ^4J=2.4 Hz), 6.80 (br tt, 1H, CF_2CF_2H, $^2J_{H,F}$=51.6 Hz, $^3J_{H,F}$=6.5 Hz), 8.14 (d, 1H, H-10, ^3J=8.7 Hz), 8.24 (d, 1H, H-4, J=1.5 Hz), 9.40 (s, 1H, OH). Anal. Calcd for $C_{19}H_{17}F_4NO_5$: C, 54.94; H, 4.13; N, 3.37. Found: C, 54.73; H, 3.91; N, 3.36.

*4.5. General procedure for pyridines **10c–g***

A solution of chromones **5c–g** (1 mmol), acetic acid (240 mg, 4.0 mmol), and β-aminocrotononitrile (165 mg, 2.0 mmol) in ethanol (5 mL) was refluxed for 0.5–4 h. After the removal of solvent under reduced pressure, the residue was purified by recrystallization from benzene or toluene to give pyridines **10c–g** as colorless crystals.

*4.5.1. 9-Chloro-5-hydroxy-2-methyl-5-(trifluoromethyl)-5H-chromeno[4,3-b]pyridine-3-carbonitrile (**10c**)*

Yield 23%, mp 192–194 °C; IR (KBr) 3417, 3098, 2237, 1589, 1550, 1482 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.87 (s, 3H, Me), 4.30 (br s, 1H, OH), 7.03 (d, 1H, H-7, ^3J=8.7 Hz), 7.40 (dd, 1H, H-8, ^3J=8.7 Hz, ^4J=2.6 Hz), 8.14 (s, 1H, H-4), 8.32 (d, 1H, H-10, ^4J=2.6 Hz). Anal. Calcd for $C_{15}H_8ClF_3N_2O_2$: C, 52.88; H, 2.37; N, 8.22. Found: C, 52.89; H, 2.25; N, 8.12.

*4.5.2. 5-Hydroxy-8-methoxy-2-methyl-5-(trifluoromethyl)-5H-chromeno[4,3-b]pyridine-3-carbonitrile (**10d**)*

Yield 24%, mp 236–238 °C; IR (KBr) 3441, 3082, 2232, 1621, 1586, 1514 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.83 (s, 3H, Me), 3.87 (s, 3H, MeO), 4.01 (br s, 1H, OH), 6.58 (d, 1H, H-7, ^4J=2.4 Hz), 6.75 (dd, 1H, H-9, ^3J=8.8 Hz, ^4J=2.4 Hz), 8.06 (s, 1H, H-4), 8.24 (d, 1H, H-10, ^3J=8.8 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 23.6 (Me), 55.8 (OMe), 96.2 (q, C-5, $^2J_{C,F}$=33.3 Hz), 101.3 (C-7), 106.2 (C-3), 110.3 (C-9), 111.1 (C-10a), 116.8 (CN), 118.6 (C-4a), 122.2 (q, CF_3, $^1J_{C,F}$=289.8 Hz), 126.5 (C-10), 139.6 (C-4), 149.5 (C-10b), 154.8 (C-6a), 163.3 (C-2), 163.9 (C-8). Anal. Calcd for $C_{16}H_{11}F_3N_2O_3$: C, 57.15; H, 3.30; N, 8.33. Found: C, 56.91; H, 3.28; N, 8.33.

*4.5.3. 5-(Difluoromethyl)-5-hydroxy-2-methyl-5H-chromeno[4,3-b]pyridine-3-carbonitrile (**10e**)*

Yield 41%, mp 212–214 °C; IR (KBr) 3421, 3093, 2232, 1589, 1556 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.78 (s, 3H, Me), 6.36 (t, 1H, CF_2H, $^2J_{H,F}$=54.2 Hz), 7.11 (dd, 1H, H-7, ^3J=8.2 Hz, ^4J=0.9 Hz), 7.19 (td, 1H, H-9, ^3J=7.6 Hz, ^4J=1.1 Hz), 7.50 (ddd, 1H, H-8, ^3J=8.3, 7.3 Hz, ^4J=1.7 Hz), 8.25 (dd, 1H, H-10, ^3J=7.8 Hz, ^4J=1.7 Hz), 8.33 (s, 1H, H-4), 8.82 (s, 1H, OH); ^{19}F NMR (376 MHz, DMSO-d_6, HFB) δ 27.67 (dd, C*F*FH, $^2J_{F,F}$=281.6 Hz, $^2J_{F,H}$=54.2 Hz), 31.95 (dd, CF*F*H, $^2J_{F,F}$=281.6 Hz, $^2J_{F,H}$=54.2 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 23.6 (Me), 96.1 (t, C-5, $^2J_{C,F}$=23.5 Hz), 107.1 (C-3), 113.6 (t, CF_2H, $^1J_{C,F}$=249.7 Hz), 116.8 (CN), 117.0 (C-7), 118.4 (C-10a), 121.2 (C-4a), 122.5 (C-9), 124.9 (C-10), 133.5 (C-8); 139.3 (C-4), 149.3 (C-10b), 153.4 (C-6a), 162.4 (C-2). Anal. Calcd for $C_{15}H_{10}F_2N_2O_2$: C, 62.50; H, 3.50; N, 9.72. Found: C, 62.49; H, 3.40; N, 9.74.

*4.5.4. 5-Hydroxy-2-methyl-5-(1,1,2,2-tetrafluoroethyl)-5H-chromeno[4,3-b]pyridine-3-carbonitrile (**10f**)*

Yield 42%, mp 193–194 °C; IR (KBr) 3384, 3264, 3081, 2233, 1613, 1601, 1587, 1554, 1493 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.80 (s, 3H, Me), 6.81 (tdd, 1H, CF_2CF_2H, $^2J_{H,F}$=51.6 Hz, $^3J_{H,F}$=7.7, 5.4 Hz), 7.10 (d, 1H, H-7, ^3J=8.2 Hz), 7.20 (ddd, 1H, H-9, ^3J=7.8, 7.3 Hz, ^4J=1.0 Hz), 7.52 (ddd, 1H, H-8, ^3J=8.2, 7.3 Hz, ^4J=1.7 Hz), 8.23 (dd, 1H, H-10, ^3J=7.8 Hz, ^4J=1.6 Hz), 8.32 (d, 1H, H-4, J=1.1 Hz), 9.54 (s, 1H, OH). Anal. Calcd for $C_{16}H_{10}F_4N_2O_2$: C, 56.81; H, 2.98; N, 8.28. Found: C, 56.75; H, 2.84; N, 8.12.

*4.5.5. 5-Hydroxy-2,9-dimethyl-5-(1,1,2,2-tetrafluoroethyl)-5H-chromeno[4,3-b]pyridine-3-carbonitrile (**10g**)*

Yield 36%, mp 220–222 °C; IR (KBr) 3416, 3086, 2232, 1614, 1592, 1556, 1496 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.34 (s, 3H, Me-9), 2.77 (s, 3H, Me-2), 6.78 (tdd, 1H, CF_2CF_2H, $^2J_{H,F}$=51.6 Hz, $^3J_{H,F}$=7.6, 5.6 Hz), 6.97 (d, 1H, H-7, ^3J=8.4 Hz), 7.31 (dd, 1H, H-8, ^3J=8.4 Hz, ^4J=2.0 Hz), 8.01 (br d, 1H, H-10, ^4J=1.5 Hz), 8.27 (s, 1H, H-4), 9.57 (br s, 1H, OH). Anal. Calcd for $C_{17}H_{12}F_4N_2O_2$: C, 57.96; H, 3.43; N, 7.95. Found: C, 57.67; H, 3.49; N, 7.62.

*4.5.6. 2-(2′-Hydroxyphenyl)-7,7-dimethyl-7,8-dihydroquinolin-5(6H)-one (**11a**)*

This compound was prepared according to procedure *A* from chromones **5a**,**e**,**f**, dimedone, and ammonium acetate. Yield 22–25%, mp 142–143 °C; IR (KBr) 1686, 1585, 1562, 1507, 1472 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.08 (s, 6H, 2Me), 2.60 (s, 2H, CH_2-6), 3.09 (s, 2H, CH_2-8), 6.94–6.98 (m, 2H, H-3′, H-5′), 7.39 (ddd, 1H, H-4′, ^3J=8.3, 7.2 Hz, ^4J=1.6 Hz), 8.08 (dd, 1H, H-6′, ^3J=8.5 Hz, ^4J=1.6 Hz), 8.22 (d, 1H, H-3, ^3J=8.6 Hz), 8.31 (d, 1H, H-4, ^3J=8.6 Hz), 13.98 (s, 1H, OH). Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.23; H, 6.47; N, 5.34.

*4.5.7. 2-(2′-Hydroxy-5′-methylphenyl)-7,7-dimethyl-7,8-dihydroquinolin-5(6H)-one (**11b**)*

This compound was prepared according to procedure *A* from chromones **5b**,**g**, dimedone, and ammonium acetate. Yield 24%, mp 193–194 °C. IR (KBr) 1686, 1618, 1582, 1563, 1492, 1455 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.07 (s, 6H, 2Me), 2.30 (s, 3H, Me), 2.60 (s, 2H, CH_2-6), 3.08 (s, 2H, CH_2-8), 6.87 (d, 1H, H-3′), 7.20 (dd, 1H, H-4′, ^3J=8.3 Hz, ^4J=1.8 Hz), 7.89 (d, 1H, H-6′, ^4J=1.8 Hz), 8.21 (d, 1H, H-3, ^3J=8.6 Hz), 8.30 (d, 1H, H-4, ^3J=8.6 Hz), 13.72 (s, 1H, OH). Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.64; H, 6.74; N, 4.87.

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