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Graphical abstract

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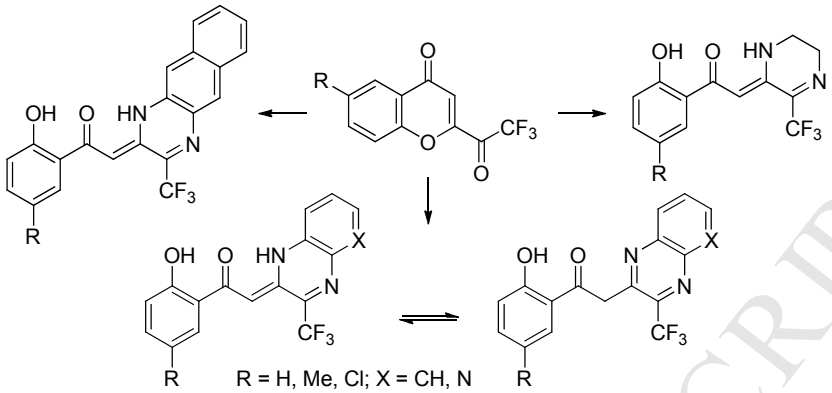

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Synthesis of 2-(trifluoroacetyl)chromones and their reactions with 1,2-diamines

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A B S T R A C T

2-(Trifluoroacetyl)chromones were obtained in good yields via the Claisen condensation of 2-hydroxyacetophenones with methyl 2-methoxytetrafluoropropionate, followed by sulfuric acid-mediated deprotection of the reaction products. These compounds react with ethylenediamine in the presence of acetic acid in methanol to produce the target 2-salicyloylmethylene-3-(trifluoromethyl)-1,2,5,6-tetrahydropyrazines in 48–61% yields. In a similar manner, their reactions with *o*-phenylenediamine and 2,3-diaminonaphthaline in refluxing acetic acid gave a mixture of ketoenamine and ketoimine tautomers of the corresponding quinoxaline derivatives in excellent yields. The regioisomeric and tautomeric composition of the pyrido[2,3-*b*]pyrazines prepared from 2-(trifluoroacetyl)chromones and 2,3-diaminopyridine was also investigated.

Keywords: Methyl 2-methoxytetrafluoropropionate; 2-(Trifluoroacetyl)chromones; 1,2-Diamines; Pyrazines; Quinoxalines.

1. Introduction

Quinoxalines are an important class of heterocyclic compounds mainly because of their pharmacological properties including antitumoral, antibacterial, antimicrobial, anticancer, anti-HIV, and other types of biological activities.[1] Trifluoromethyl-substituted quinoxalines have also drawn considerable attention because they often show unique biological and physiological activities.[2]

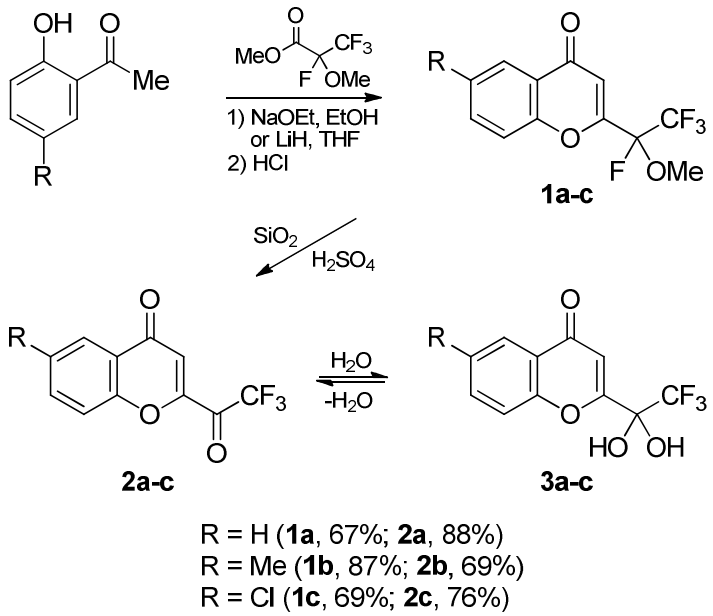
These compounds are primarily prepared by the reactions of substituted *o*-phenylenediamines with CF_3-containing α-diketones and their derivatives,[3] perfluorinated epoxides,[4] fluorinated α-halo(nitroso)-β-dicarbonyl compounds,[5] trifluoropyruvaldehyde,[6] and ethyl trifluoropyruvate.[7] The latter reaction involves the intermolecular condensation of a variety of 1,2-diamines with the α-keto group of the ester to produce an intermediate imine, which undergoes intramolecular cyclization to afford the corresponding 3-substituted quinoxalinone derivatives. The parent 2-CF_3-quinoxaline has been synthesized by the condensation of 3-(2,2-dimethylhydrazono)-1,1,1-trifluoro-2-propanone (synthetic equivalent of trifluoropyruvaldehyde) with *o*-phenylenediamine.[8]

Apart from these approaches towards the synthesis of trifluoromethylated quinoxalines, a simple procedure for their preparation from 2-(trifluoroacethyl)chromones and *o*-phenylenediamine, has been developed by us recently.[9] This reaction is the first example of conversion of the chromone system to CF_3-containing quinoxalines and deserves further investigations in order to expand the scope of its possible applications. Given the broad utility of trifluoromethylated heterocycles in medicinal chemistry[10,11] and continuing our research in this field,[9,12] we have extended our experiments to a number of 2-CF_3CO-chromones as building blocks and such binucleophilic reagents as 1,2-diamines for the preparation of novel trifluoromethylated pyrazine and quinoxaline derivatives. We discuss here the products of these reaction and in particular the regioisomeric and tautomeric composition of the pyrido[2,3-*b*]pyrazines prepared from 2,3-diaminopyridine.

2. Results and discussion

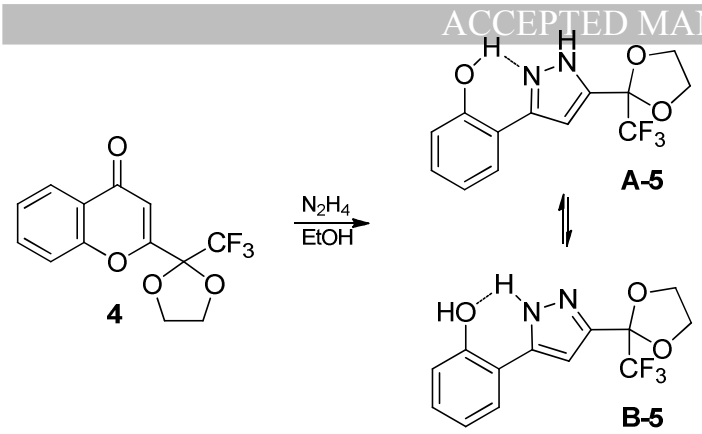
It was found that methyl 2-methoxytetrafluoropropionate, easily prepared from hexafluoropropene epoxide and methanol,[13,14] reacted with 2-hydroxyacetophenones under Claisen reaction conditions (refluxing ethanol and NaOEt as catalyst or refluxing THF and LiH as catalyst) affording, after hydrochloric acid hydrolysis, chromones **1a–c** in 67–87% yields. Deprotection of chromones **1a–c** was carried out using 96% H_2SO_4 and SiO_2,[14] to afford 2-(trifluoroacetyl)chromones **2a–c** in 76–88% yields (Scheme 1). In marked contrast to the known 2-

acetylchromones,[15] chromones **2a–c** obtained in this work mainly exist in the *gem*-diol form **3**, as was observed in the case of 3-(trifluoroacetyl)chromones[12] and 3-(trifluoroacetyl)coumarins.[16]



Scheme 1. Synthesis of chromones **1** and **2**.

It is necessary to mention that an attempt to use a 1,3-dioxolane protecting group for the preparation of 2-(trifluoroacetyl)chromones **2** was not successful. In this case, chromone **4**, prepared from methyl 2-(trifluoromethyl)-1,3-dioxolane-2-carboxylate[17] and 2-hydroxyacetophenone in the presence of NaOEt, turned out to be very stable under various conditions and was recovered unchanged after treatment with such catalysts as hydrochloric acid, a mixture of HCl and AcOH, 60% H_2SO_4, and BBr_3 in dichloromethane. While chromone **4** did not react with hydroxylamine, methylhydrazine, phenylhydrazine, and *o*-phenylenediamine in refluxing ethanol (only starting material was recovered), its reactions with hydrazine hydrate under the same conditions gave pyrazole **5** in 77% yields (Scheme 2).

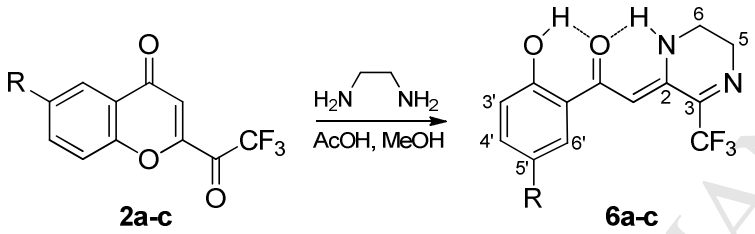


Scheme 2. Reaction of chromone **4** with hydrazine.

The ^{1}H NMR spectrum of **5** in a DMSO-d_6 solution showed two sets of signals due to the possibility of annular prototropy of the pyrazole ring. Thus, four signals exhibiting broadening at higher frequency values were observed, indicating that pyrazole **5** exists in DMSO-d_6 as a 7:3 mixture of tautomers **A-5** and **B-5**, respectively, due to the presence of intramolecular hydrogen bonds in each tautomer (OH···N and NH···O). The structural assignments were based on the signals due to the NH and OH protons at δ_{NH} = 10.3, δ_{OH} = 13.1 ppm (tautomer **A-5**) and δ_{OH} = 10.5, δ_{NH} = 13.7 ppm (tautomer **B-5**).[18] Tautomer **A-5** is the more abundant (70%) since its intramolecular O–H···N=C hydrogen bond is stronger than the intramolecular N–H···O–C hydrogen bond in tautomer **B-5**. Unexpectedly lower reactivity of chromone **4**, compared with the unsubstituted chromone,[19] appeared to be a result of the steric effect of the 1,3-dioxolane group.

Published data on the reactions of 2-substituted chromones with 1,2-diamines are scarce. Only one report is known which describes the reaction of ethyl chromone-2-carboxylates with *o*-phenylenediamine to give the corresponding 2-quinoxalinones.[20] To demonstrate the ability of 2-(trifluoroacetyl)chromones **2** to undergo regioselective heterocyclization reactions, chromones **2** were reacted with aliphatic, aromatic and heterocyclic diamines such as ethylenediamine, *o*-phenylenediamine, 2,3-diaminonaphthalene, and 2,3-diaminopyridine. Our results showed that these compounds behave as a latent 1,2-diketone, having a masked salicyloyl fragment, and react with diamines to give various pyrazine and quinoxaline derivatives in good yields.

The study of reaction of 2-CF_3CO-chromones **2**, existing principally as the hydrates **3**, with diamines was initiated with ethylenediamine. Several competing pathways for the reaction in both the initial step of nucleophilic attack and the subsequent heterocyclization would have been expected. However, we found that the principal direction of the reaction in acidic medium is the formation of 1-aryl-2-(3-trifluoromethyl-5,6-dihydropyrazin-2-ylidene)ethanones **6a–c**. When chromones **2a–c** were treated with ethylenediamine in the presence of acetic acid in MeOH at room temperature for 48 h, pyrazines **6a–c** were isolated in 48–61% yields as orange crystals. The driving force for the process is the stabilization of the *Z*-enamines **6** by two hydrogen bonds between the carbonyl oxygen and the hydrogens of the NH and OH groups (Scheme 3).



2a-c **6a-c**

R	**6**	Yield (%)
H	**a**	57
Me	**b**	61
Cl	**c**	48

Scheme 3. Synthesis of compounds **6**.

The structure of the products **6a–c** was established by the usual spectral analyses. A characteristic feature of their ^{1}H NMR spectra in a DMSO-d_6 solution is the appearance of three singlets at δ 6.13–6.22, 10.44–10.54, and 12.03–12.70 ppm for the =CH, NH, and OH protons, respectively, in good accordance with the given structure. All signals in the ^{1}H and ^{13}C NMR spectra of compound **6c** were assigned on the basis of 2D ^{1}H–^{13}C HSQC, HMBC, and ^{1}H–^{1}H NOESY experiments; as expected, the latter showed the NOE correlation between =CH and H-6′ protons. Interestingly, the CF_3 group in the ^{19}F NMR spectrum of **6c** in $CDCl_3$ manifests itself as a quartet (doublet of triplets) at δ 95.2 ppm ($^5J_{F,H}$ = 1.5 Hz) due to coupling with the =CH and CH_2-5 protons. This fact was established by means of the ^{19}F{^{1}H} double resonance techniques (Fig. 1).

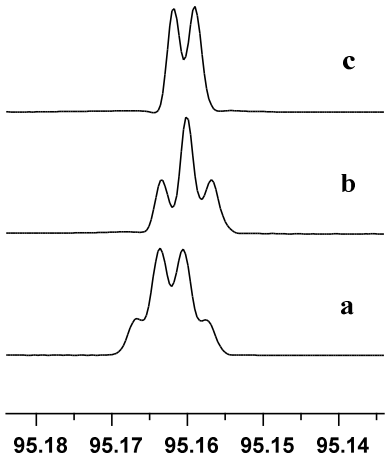
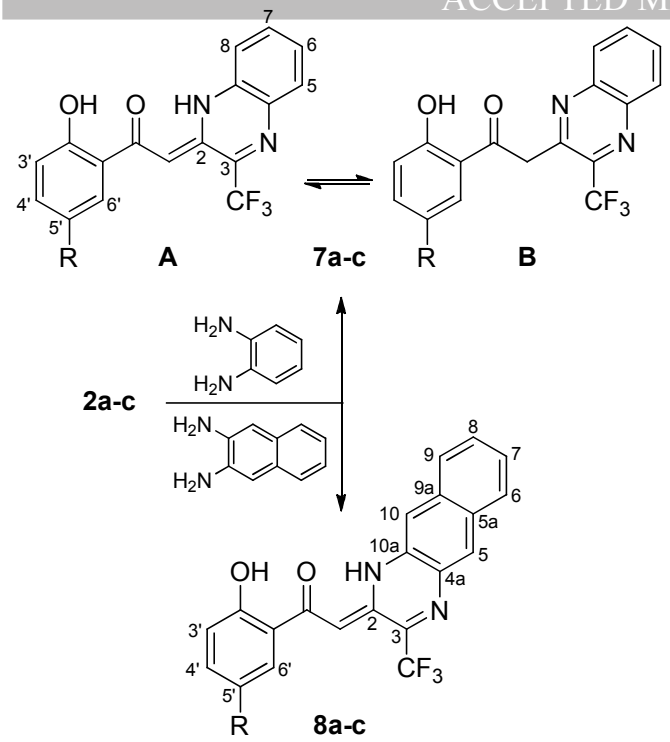


Fig. 1. $^{19}F\{^{1}H\}$ double-resonance experiment (470.5 MHz, $CDCl_3$) of compound **6c**: (a) normal spectrum ^{19}F, (b) with =CH decoupled, (c) with CH_2-5 decoupled.

In contrast to ethylenediamine, reactions of chromones **2** with *o*-phenylenediamine afforded a mixture of two tautomeric forms **A-7** and **B-7** as was observed previously for 2-ketomethylquinolines.[21] Indeed, we found that chromones **2a–c** reacted with *o*-phenylenediamine in refluxing acetic acid for 4 h to give products **7a–c** as a mixture of enamine and imine tautomers (**A** and **B** as red or orange crystals) in 79–87% yields (Scheme 4). The complete ^{1}H and ^{13}C NMR assignments of enamine (**A**) and imine (**B**) forms of quinoxaline **7a** were made by a combination of 2D ^{1}H–^{1}H COSY, ^{1}H–^{13}C HSQC and HMBC experiments. In the ^{19}F NMR spectra of **7a–c**, the CF_3 group of tautomer **A** appeared as a doublet ($^{5}J_{F,H}$ = 1.6–1.8 Hz) at 96.1–96.4 ppm and the CF_3 group of **B** appeared as a triplet ($^{5}J_{F,H}$ = 1.3–1.4 Hz) at 98.8–98.9 ppm (DMSO-d_6, C_6F_6). It is worth noting that protected chromone **1b** did not react with ethylenediamine and *o*-phenylenediamine under various acidic conditions and was recovered unchanged.



R	7	A:B	Yield (%)	8	Yield (%)
H	**a**	40:60	83	**a**	88
Me	**b**	42:58	79	**b**	80
Cl	**c**	58:42	87	**c**	98

Scheme 4. Synthesis of compounds **7** and **8**.

Under similar conditions, 2,3-diaminonaphthalene gave benzo[*g*]quinoxaline **8a–c** in excellent yields (80–98%). According to the ^{1}H, ^{19}F, and ^{13}C NMR spectra, these compounds are predominantly in the form of enamine tautomer, probably because of the additional benzene ring (Scheme 4). All signals in the ^{1}H and ^{13}C NMR spectra of compound **8a** were assigned on the basis of 2D ^{1}H–^{1}H COSY, NOESY, and ^{1}H–^{13}C HSQC, and HMBC experiments. The key NOE correlations demonstrate the spatial contiguity of =CH to H-6′ and NH to H-10. In the ^{19}F NMR spectrum of **8a**, the CF_3 group appeared as a doublet at δ 93.8 ppm ($CDCl_3$) with $^{5}J_{F,H}$ = 1.6 Hz due to coupling with the =CH proton. Since only one structural isomer can be produced in reactions involving the symmetrical diamines such as ethylenediamine, *o*-phenylenediamine, and 2,3-diaminonaphthalene, the structures of the products **6–8** require no special discussion. Our attempts to prepare the corresponding quinoxaline derivative from chromone **2b** and 1,2-diamino-4,5-

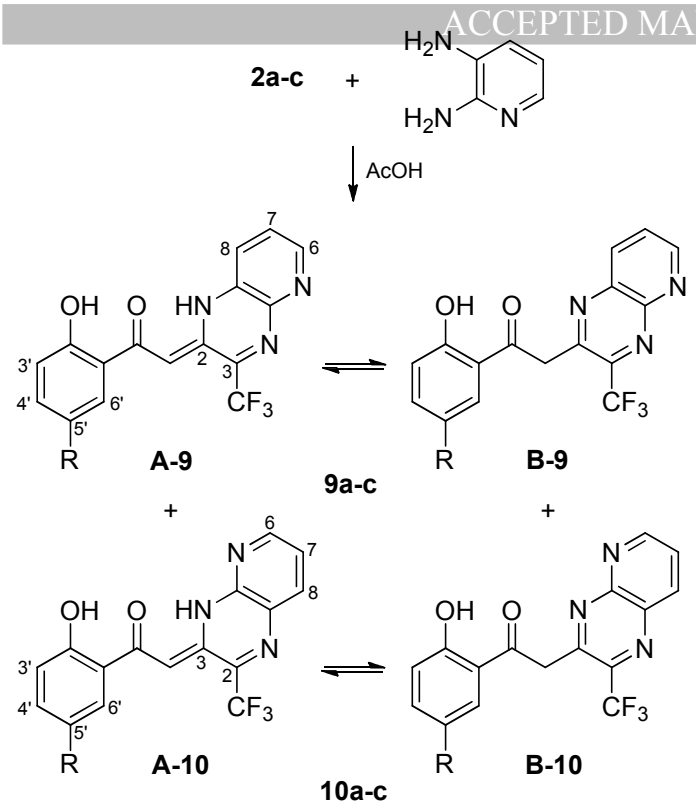
difluorobenzene in refluxing acetic acid or *n*-butanol were fruitless. In all cases, only starting material was recovered due to the less nucleophilic character of this diamine.

Next, we decided to determine the regiochemistry of the condensation when run on a diamine that could lead to structurally isomeric products. When 2,3-diaminopyridine was used under the same conditions (AcOH, reflux, 4 h), the reactions with chromones **2a–c** proceeded smoothly to provide high yields of mixtures of two regioisomeric pairs (**A-9**+**B-9** and **A-10**+**B-10**); different ratios of enamine regioisomers **A-9** and **A-10** as well as their imine tautomers **B-9** and **B-10** were observed (Scheme 5, Table 1, structure assignments see below). The proportions of these tautomers were determined by integration of the CF_3 signals in the ^{19}F NMR spectra. Note that in the case of chromone **2c**, tautomer **B-10** was not found in the crude reaction mixture. While in the solid state compounds **9** and **10** were rather stable and could be stored at room temperature for a long time, in $CDCl_3$ solution they underwent reversible tautomerism and exist as an equilibrium mixture of the four isomers. As can be seen from Table 1, a composition ratio of the tautomeric pair **A-10**+**B-10** did not change when a solution in $CDCl_3$ in the presence of a catalytic amount of AcOH was allowed to stand at ambient temperature for 25 h, while the equilibrium between tautomers **A-9** and **B-9** significantly shifted towards imine tautomer **B** and remained unchanged for 40 h. The reason for the different behavior of enamine forms **A-9** and **A-10** should be studied further.

Table 1. Ratio and yield of regioisomers **9** and **10**.[a]

9, **10**	R	Yield (%)	**9**:**10**	**A-9**:**B-9**[b]	**A-10**:**B-10**[b]	**A-9**:**B-9**[c]	**A-10**:**B-10**[c]
a	H	88	40:60	38:2	56:4	9:31	56:4
b	Me	91	78:22	73:5	20:2	14:64	20:2
c	Cl	98	85:15	69:16	15:0	25:60	15:0

[a] Obtained in refluxing AcOH for 4 h.
[b] After 15 min in DMSO-d_6.
[c] At equilibrium after 25 h in DMSO-d_6.



Scheme 5. Synthesis of compounds **9** and **10**.

All signals in the ^{1}H and ^{13}C NMR spectra of the isomeric mixture **9a+10a** were assigned on the basis of 2D COSY, HSQC and HMBC experiments. To determine the regiochemistry and to verify the assignment in compounds of type **9** and **10**, 2D NOESY spectra of mixtures **9a,b+10a,b** were recorded. They exhibit an intensive cross-peak between the NH and H-8 protons for isomer **A-9** and do not show any connectivities between these protons for **A-10**. These results clearly demonstrate that structure **A-9** is the derivative of 3-(trifluoromethyl)pyrido[2,3-*b*]pyrazine (**11**), while structure **A-10** – 2-(trifluoromethyl)pyrido[2,3-*b*]pyrazine (**12**). It should be noted that in the NOESY spectra of **9+10**, two very weak cross-peaks between the NH and =CH protons for **A-9** and **A-10** were also observed, probably due to the tautomeric equilibrium.

Moreover, the assignment of structure **A-9** to the 3-CF_3-isomer and **A-10** to the 2-CF_3-isomer is based on the ^{13}C NMR chemical shifts for C-2 and C-3 in their imine tautomers **B-9** and **B-10**. A comparison of these chemical shifts with the data reported for parent systems **11** and **12**[6] confirms the validity of the structures (the α-substituent effect of the methyl group is 9.3, while the β-substituent effect is 0.6)[22] (Fig. 2).

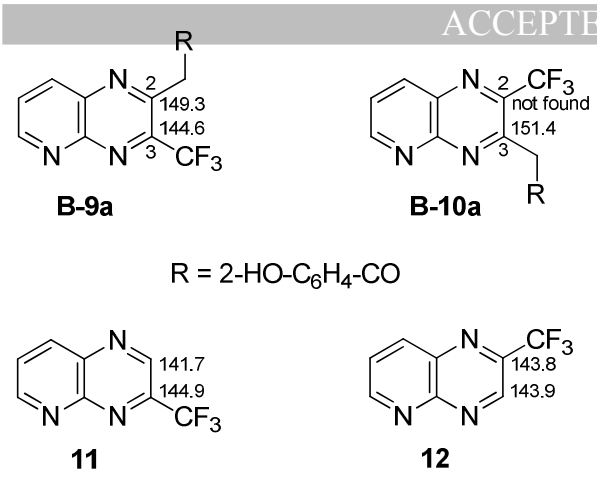


Fig. 2. Diagnostic ^{13}C NMR signals (δ, ppm, $CDCl_3$) of 2- and 3-CF_3-pyrido[2,3-*b*]pyrazines.

The significant ^1H NMR chemical shifts of the pyridine protons H-6, H-7, and H-8 compiled in Table 2 suggest differences in the regiochemistry, especially for **A-9** and **A-10** due to the NH group in the fused pyrazine ring. For the major isomer **A-9**, the pyridine H-8 proton is shifted upfield to about 7.7 ppm. This is another feature which differentiates the regioisomers. The ^1H NMR spectrum of the equilibrium mixture **9a+10a**, recorded in $CDCl_3$, is reported in Fig. 3, as a representative example. It shows that the reaction between 2-CF_3CO-chromones **2** and 2,3-diaminopyridine proceeds very cleanly without any undesirable side-products.

Table 2. Pyridine protons of regioisomers **9** and **10** (^1H NMR, δ, ppm, $CDCl_3$).

9, **10**	**A-9**			**B-9**		
	H-6	H-7	H-8	H-6	H-7	H-8
a	8.70	7.59	7.74	9.31	7.87	8.50
b	8.69	7.58	7.74	9.31	7.87	8.50
c	8.75	7.62	7.79	9.33	7.88	8.50
	A-10			**B-10**		
a	8.60	7.31	8.10	9.32	7.86	8.63
b	8.59	7.31	8.10	9.31	7.87	8.63
c	8.64	7.36	8.15	–	–	–

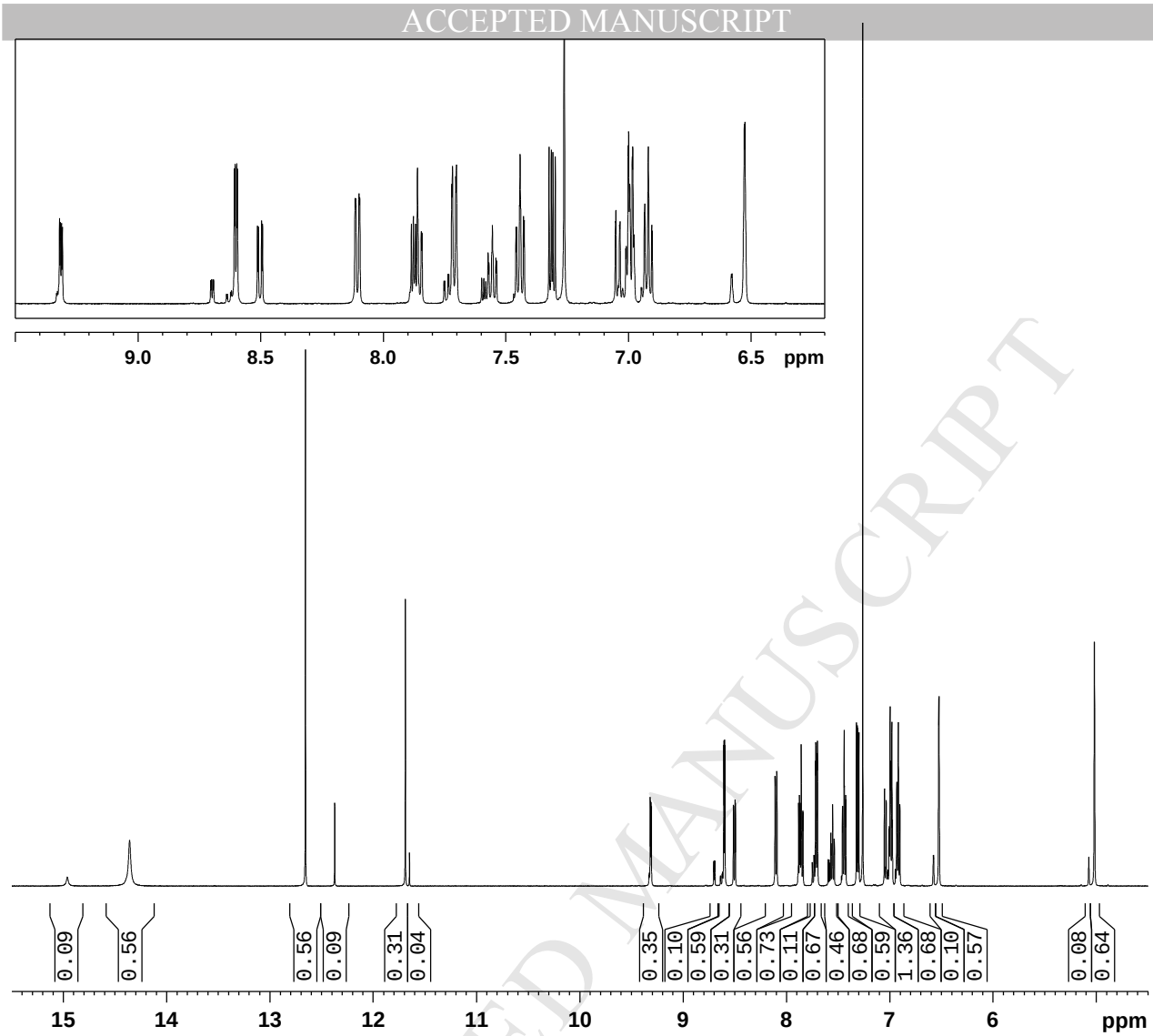


Fig. 3. ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of the equilibrium mixture of **9a** and **10a**.

We also found that the reaction conditions were very important for the regioselectivity of this reaction. Thus, when chromones **2a–c** were reacted with 2,3-diaminopyridine in acetic acid at room temperature within one week, only 3-CF_3-isomers **A-9** and **B-9** precipitated from the reaction mixture and a simple filtration provides analytically pure products in all cases. Additional crystalline material represented by the tautomer **B-9**, along with the minor amounts of **A-9** and **A-10**, could be obtained from the mother liquor (Table 3). As expected, if pure enamine **A-9b**, prepared at room temperature, is refluxed in AcOH, the amount of imine form **B-9** increases at the expense of **A-9** (**A-9**:**B-9** = 35:65 after 4 h in boiling AcOH and 18:82 after standing additional 21 h at room temperature in $CDCl_3$ in the presence of AcOH). Note that without addition of AcOH as a

catalyst pure compound **A-9b** underwent tautomeric conversion into the equilibrium mixture (**A-9**:**B-9** = 18:82) during ca. 140 h, i.e. this process required a much longer reaction time.

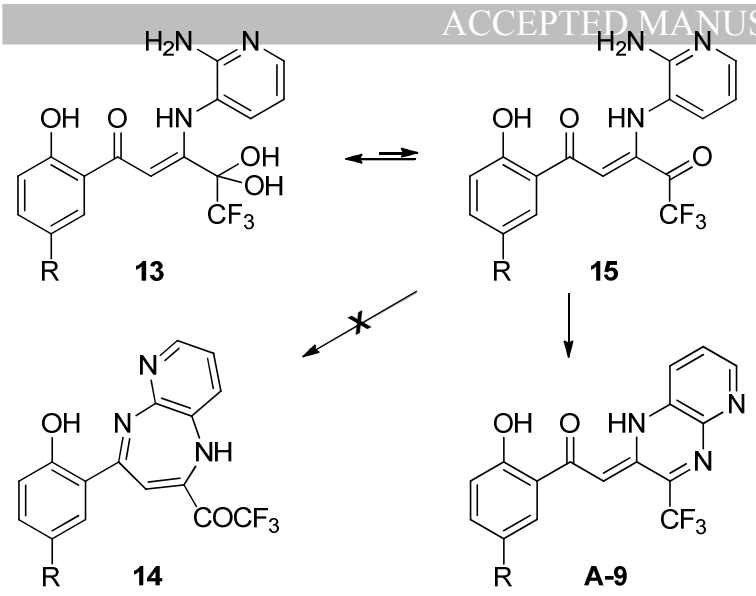
Table 3. Ratio and yield of regioisomers **9** and **10**.[a]

9, **10**	R	**A-9**:**B-9**:**A-10**:**B-10**[b]	Yield	**A-9**:**B-9**:**A-10**:**B-10**[c]	Yield	Total yield
a	H	24:76:0:0	52 mg (34%)	18:66:15:1	78 mg (51%)	130 mg (85%)
b	Me	98:2:0:0	73 mg (48%)	16:72:12:0	63 mg (41%)	136 mg (89%)
c	Cl	30:66:4:0	84 mg (56%)	23:51:26:0	59 mg (39%)	143 mg (95%)

[a] Obtained in AcOH at r.t. for one week from 120 mg of the starting chromone **2**.
[b] Composition of the initially formed precipitate.
[c] Composition of the precipitate from the mother liquor.

Thus, the first step of the reaction leading to a mixture of regioisomers **9** and **10** apparently involves an attack of the more nucleophilic 3-NH_2 group at C-2 of **2** with concomitant opening of the pyrone ring (1,4-addition, intermediate **13**). Subsequent intramolecular attack of the less nucleophilic 2-NH_2 group at the trifluoroacetyl group leads to pyrido[2,3-*b*]pyrazines **A-9**. The alternative cyclization of **13**, involving the amino group and the carbonyl carbon atom connected to the benzene ring, does not occur, and no formation of the corresponding pyrido[2,3-*b*][1,4]diazepines **14** was detected (Scheme 6).

The formation of **9** as the major product can be rationalized if it is assumed that the equilibrium between chromone **2** and its hydrate **3** largely favors **3**, so that the keto function is protected as a hydrate and the C-2 atom of **2** reacts preferentially with the more nucleophilic 3-NH_2 group of the starting diamine to give intermediate **13**, which is in equilibrium with small amounts of the ketone **15**. The ketone carbonyl of **15** would then react with the less nucleophilic 2-NH_2 group, yielding the observed major product **A-9** (Scheme 6). In an attempt to gain evidence regarding the position of equilibrium between **2** and **3**, the ^{19}F NMR spectra of **3a,b** in CD_3CO_2D was examined. This revealed only one singlet at 80.2 ppm, which is consistent with the attachment of the CF_3 group to the sp^3-hybridized carbon atom. In addition, the ^1H NMR spectra of these solutions did not display signals of non-hydrated chromone protons. These results indicate that the major species actually present in acetic acid is the unreactive hydrate **3**. Although chromones **2** were not observed spectroscopically in CD_3CO_2D, their presence is implied by the overall reaction.



Scheme 6. Plausible route of the reaction.

These results clearly indicate that C-2 of chromones **2**, due to the electron-withdrawing effect of the CF_3CO and/or $CF_3C(OH)_2$ groups, is very susceptible to nucleophilic attack, which makes them useful for constructing highly functionalized biologically and medicinally important products. Since many natural products are based on the quinoxaline structure, this reaction offers the potential as an entry to the synthesis of trifluoromethylated analogs of these compounds.

3. Conclusion

In summary, we have developed a simple and convenient two-step synthesis of 2-(trifluoroacetyl)chromones starting from commercially available 2-hydroxyacetophenones and hexafluoropropene epoxide via introduction of a CF_3COCO moiety into a ketone methyl group. The chromones obtained are of interest as precursors for the synthesis of various trifluoromethylated pyrazine and quinoxaline derivatives. The latter can exist as a mixture of two tautomeric forms and result from the initial nucleophilic 1,4-addition of a 1,2-diamine to the C-2 atom of 2-(trifluoroacetyl)chromones. Further studies on the synthetic application of this methodology and on the reactivity of the described chromones are in progress.

4. Experimental

4.1. General

^{1}H, ^{19}F, and ^{13}C NMR spectra were recorded on Bruker DRX-400 (400, 376, 100 MHz) and AVANCE-500 (500, 470.5, 126 MHz) spectrometers in DMSO-d_6 or $CDCl_3$ with TMS and C_6F_6 as internal standards. IR spectra were recorded on a Perkin-Elmer Spectrum BX-II as KBr discs and Nicolet 6700 instruments (FTIR mode). Elemental analyses were performed at the Microanalysis Services of the Institute of Organic Synthesis, Ural Branch, Russian Academy of Sciences. All solvents used were dried and distilled per standard procedures.

4.2. General procedure for the synthesis of compounds 1a–c

*4.2.1. 2-(1,2,2,2-Tetrafluoro-1-methoxyethyl)chromone (**1a**).* Method *A*. A mixture of methyl 2-methoxytetrafluoropropionate (25.0 g, 131.5 mmol) and 2-hydroxyacetophenone (17.4 g, 127.8 mmol) was added dropwise to an alcoholic solution of NaOEt obtained by dissolution of sodium (8.6 g, 374.1 mmol) in anhydrous EtOH (150 mL). The resulting reaction mixture was heated at reflux with stirring for 5 h. Concentrated HCl (65 mL) was added to the disodium salt, and the mixture was heated at reflux with stirring for 1 h. The cooled mixture was quenched by addition of water (200 mL) and the solvent concentrated under reduced pressure. The organic product thus obtained was extracted with ether (3 × 100 mL) and the combined extracts were washed with 5% KOH (60 mL) and water (60 mL), dried over anhydrous $MgSO_4$, and evaporated to afford a colourless solid. The solid was recrystallized from hexane–ether (10:1) to give **1a** in 57% yield (20.0 g), mp 96–97 °C.

Method *B*. A solution of methyl 2-methoxytetrafluoropropionate (6.0 g, 31.6 mmol) and 2-hydroxyacetophenone (3.9 g, 28.7 mmol) in THF (15 mL) was added dropwise to a suspension of LiH (1.0 g, 125.0 mmol) in THF (40 mL). The resulting reaction mixture was heated at reflux with stirring for 6 h. After that, the mixture was concentrated under reduced pressure, the residue was dissolved in AcOH (40 mL) and concentrated H_2SO_4 (10 mL), stirred for 30–40 min and poured onto ice (200 g). The solid obtained was filtered off, dried, and recrystallized from heptane to give **1a** in 67% yield (5.3 g), mp 96–97 °C. IR (ATR) 1660, 1610, 1463, 1386, 1327 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.60 (d, $^{4}J_{H,F}$ = 0.8 Hz, 3H, MeO), 6.77 (d, $^{4}J_{H,F}$ = 1.8 Hz, 1H, H-3), 7.49 (ddd, *J* = 8.0, 7.2, 1.0 Hz, 1H, H-6), 7.56 (dd, *J* = 8.5, 1.0 Hz, 1H, H-8), 7.76 (ddd, *J* = 8.5, 7.2, 1.7 Hz, 1H, H-7), 8.23 (dd, *J* = 8.0, 1.7 Hz, 1H, H-5); ^{19}F NMR (376 MHz, $CDCl_3$) δ 25.1 (m, F), 79.9 (d, $^{3}J_{F,F}$ = 4.0 Hz, CF_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 53.2 (d, *J* = 3.4 Hz), 113.8 (d, *J* = 3.9 Hz), 118.4, 119.5 (qd, *J* = 287.1, 35.1 Hz), 124.1, 126.0, 126.4, 134.7, 155.0, 155.3, 156.2, 177.1; MS (EI), *m/z*

(%) 276 $[M]^+$ (100), 207 $[M–CF_3]^+$ (100). Anal. Calcd for $C_{12}H_8F_4O_3$: C, 52.19; H, 2.92. Found: C, 52.16; H, 3.30.

*4.2.2. 6-Methyl-2-(1,2,2,2-tetrafluoro-1-methoxyethyl)chromone (**1b**).* This compound was prepared from methyl 2-methoxytetrafluoropropionate (6.0 g, 31.6 mmol) and 2-hydroxy-5-methylacetophenone (4.4 g, 29.3 mmol) in the presence of LiH (1.0 g, 125.0 mmol) according to method *B*. Yield 7.2 g (87%), mp 107–108 °C. IR (ATR) 1651, 1615, 1482, 1433, 1371, 1330 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.48 (s, 3H, Me), 3.59 (d, $^4J_{H,F}$ = 0.8 Hz, 3H, MeO), 6.74 (d, $^4J_{H,F}$ = 1.8 Hz, 1H, H-3), 7.45 (d, J = 8.6 Hz, 1H, H-8), 7.56 (dd, J = 8.6, 2.2 Hz, 1H, H-7), 8.00 (br d, J = 2.0 Hz, 1H, H-5); ^{19}F NMR (376 MHz, $CDCl_3$) δ 24.9 (m, F), 79.8 (d, $^3J_{F,F}$ = 4.0 Hz, CF_3). Anal. Calcd for $C_{13}H_{10}F_4O_3$: C, 53.80; H, 3.47. Found: C, 53.91; H, 3.49.

*4.2.3. 6-Chloro-2-(1,2,2,2-tetrafluoro-1-methoxyethyl)chromone (**1c**).* This compound was prepared from methyl 2-methoxytetrafluoropropionate (6.0 g, 31.6 mmol) and 5-chloro-2-hydroxyacetophenone (4.9 g, 28.7 mmol) in the presence of LiH (1.0 g, 125.0 mmol) according to method *B*. Yield 6.2 g (69%), mp 101–102 °C. IR (ATR) 1653, 1605, 1467, 1438, 1371, 1323 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.60 (d, $^4J_{H,F}$ = 0.8 Hz, 3H, MeO), 6.77 (d, $^4J_{H,F}$ = 1.7 Hz, 1H, H-3), 7.52 (d, J = 9.0 Hz, 1H, H-8), 7.70 (dd, J = 9.0, 2.6 Hz, 1H, H-7), 8.18 (d, J = 2.6 Hz, 1H, H-5); ^{19}F NMR (376 MHz, $CDCl_3$) δ 24.9 (m, F), 80.0 (d, $^3J_{F,F}$ = 4.2 Hz, CF_3). Anal. Calcd for $C_{12}H_7ClF_4O_3$: C, 46.40; H, 2.27. Found: C, 46.70; H, 2.25.

4.3. Compounds 2a–c, 4 and 5

*4.3.1. 2-(Trifluoroacetyl)chromone (**2a**) and 2-(2,2,2-trifluoro-1,1-dihydroxyethyl)chromone (**3a**).* To a suspension of SiO_2 (850 mg, 14.2 mmol) in concentrated sulfuric acid (22 mL) chromone **1a** (11.7 g, 42.4 mmol) was added in small portions with stirring. The resulting yellow solution was heated with stirring at 125–130 °C for 1 h. The cooled mixture was poured into water (300 mL) and extracted with ethyl acetate (4 × 50 mL). The combined extracts were washed with water (3 × 50 mL) and evaporated under reduced pressure. The solid that formed was recrystallized from toluene–ethyl acetate (5:1) to give **2a** in 88% yield (9.0 g), mp 158 °C. IR (KBr) 3288, 1636, 1617, 1584, 1568, 1482 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (**2a**, 83%) δ 7.18 (s, 1H, H-3), 7.52 (ddd, J = 8.0, 7.2, 1.0 Hz, 1H, H-6), 7.62 (dd, J = 8.6, 1.0 Hz, 1H, H-8), 7.81 (ddd, J = 8.6, 7.2, 1.7 Hz, 1H, H-7), 8.22 (dd, J = 8.0, 1.7 Hz, 1H, H-5); (**3a**, 17%) 6.84 (s, 1H, H-3), 6.87 (s, 2H, 2OH), 7.45 (ddd, J = 8.0, 7.2, 1.0 Hz, 1H, H-6), 7.50 (d, J = 8.6 Hz, 1H, H-8), 7.71 (ddd, J = 8.6, 7.2, 1.7 Hz, 1H, H-7), 8.18 (dd, J = 8.0, 1.6 Hz, 1H, H-5); ^1H NMR (400 MHz, DMSO-d_6) (**3a**, 100%) δ 6.64 (s, 1H, H-3), 7.54 (ddd, J = 8.0, 7.2, 1.0 Hz, 1H, H-6), 7.69 (dd, J = 8.5, 1.0 Hz, 1H, H-8), 7.86 (ddd, J = 8.5, 7.2,

1.7 Hz, 1H, H-7), 8.07 (dd, *J* = 8.0, 1.7 Hz, 1H, H-5), 8.37 (s, 2H, 2OH); ^{19}F NMR (376 MHz, DMSO-d_6) δ80.8 (s, CF_3); ^{1}H NMR (500 MHz, CD_3CO_2D) (**3a**, 100%) δ7.03 (s, 1H, H-3), 7.53 (t, *J* = 7.6 Hz, 1H, H-6), 7.67 (d, *J* = 8.5 Hz, 1H, H-8), 7.85 (ddd, *J* = 8.5, 7.3, 1.7 Hz, 1H, H-7), 8.22 (dd, *J* = 8.1, 1.7 Hz, 1H, H-5), 8.37 (s, 2H, 2OH); ^{19}F NMR (470.5 MHz, CD_3CO_2D) δ80.2 (s, CF_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ90.8 (q, *J* = 32.5 Hz), 110.3, 118.6, 122.5 (q, *J* = 290.0 Hz), 123.1, 125.0, 126.0, 134.9, 155.6, 163.1, 177.0; MS (EI), *m/z* (%) 242 $[M]^+$ (100), 173 $[M–CF_3]^+$ (36), 145 $[M–COCF_3]^+$ (33), 101 (10), 92 (8), 89 (43), 69 $[CF_3]^+$ (8). Anal. Calcd for $C_{11}H_5F_3O_3\cdot H_2O$: C, 50.78; H, 2.71. Found: C, 50.76; H, 2.35.

*4.3.2. 6-Methyl-2-(trifluoroacetyl)chromone (**2b**).* This compound was prepared as a covalent hydrate **3b** from chromone **1b** according to the procedure described for compound **2a**. Yield 3.5 g (69%), mp 173–174 °C. IR (KBr) 3317, 1642, 1594, 1488 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.44 (s, 3H, Me), 6.60 (s, 1H, H-3), 7.59 (d, *J* = 8.6 Hz, 1H, H-8), 7.67 (dd, *J* = 8.6, 2.2 Hz, 1H, H-7), 7.85 (dq, *J* = 2.2, 0.5 Hz, 1H, H-5), 8.35 (s, 2H, 2OH); ^{19}F NMR (376 MHz, DMSO-d_6) δ80.8 (s, CF_3). ^{19}F NMR (470.5 MHz, CD_3CO_2D) δ80.2 (s, CF_3). Anal. Calcd for $C_{12}H_7F_3O_3\cdot H_2O$: C, 52.56; H, 3.31. Found: C, 52.67; H, 3.32.

*4.3.3. 6-Chloro-2-(trifluoroacetyl)chromone (**2c**).* This compound was prepared as a covalent hydrate **3c** from chromone **1c** according to the procedure described for compound **2a**. Yield 4.0 g (76%), mp 140–141 °C. IR (KBr) 3340, 1639, 1614, 1597, 1571, 1470 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ6.66 (s, 1H, H-3), 7.77 (d, *J* = 9.0 Hz, 1H, H-8), 7.89 (d, *J* = 9.0, 2.7 Hz, 1H, H-7), 8.00 (d, *J* = 2.7 Hz, 1H, H-5), 8.42 (s, 2H, 2OH); ^{19}F NMR (376 MHz, DMSO-d_6) δ80.9 (s, CF_3). Anal. Calcd for $C_{11}H_4ClF_3O_3\cdot H_2O$: C, 44.84; H, 2.05. Found: C, 44.84; H, 2.03.

*4.3.4. 2-(2-Trifluoromethyl-1,3-dioxolan-2-yl)chromone (**4**).* A mixture of 2-trifluoromethyl-[1,3]dioxolane-2-carboxylic acid methyl ester (12.3 g, 61.5 mmol) and 2-hydroxyacetophenone (7.6 g, 55.8 mmol) was added dropwise to an alcoholic solution of NaOEt obtained by dissolution of sodium (5.2 g, 226.2 mmol) in anhydrous EtOH (100 mL). The resulting reaction mixture was heated at reflux with stirring for 5 h. Concentrated HCl (40 mL) was added to the disodium salt, and the mixture was heated at reflux with stirring for 40 min. The cooled mixture was quenched by addition of water (125 mL) and the solvent concentrated under reduced pressure. The solid was filtered off, washed with wated, and dried to give chromone **4** in 74% yield (13.0 g), mp 103–104 °C. IR (ATR) 1659, 1610, 1574, 1467, 1392, 1315 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ4.18–4.26 (m, 2H, CH_2), 4.30–4.38 (m, 2H, CH_2), 6.75 (s, 1H, H-3), 7.44 (ddd, *J* = 8.0, 7.2, 1.0 Hz, 1H, H-6), 7.54 (dd, *J* = 8.5, 1.0 Hz, 1H, H-8), 7.72 (ddd, *J* = 8.5, 7.2, 1.7 Hz, 1H, H-7), 8.20 (dd, *J* = 8.0, 1.7

Hz, 1H, H-5); ^{19}F NMR (376 MHz, $CDCl_3$) δ 81.3 (s, CF_3); MS (EI): *m/z* (%) 286 $[M]^+$ (57), 217 $[M\text{-}CF_3]^+$ (100), 173 (14), 145 $[M\text{-}CF_3C(OCH_2)_2]^+$ (27), 89 (25), 69 $[CF_3]^+$ (10). Anal. Calcd for $C_{13}H_9F_3O_4$: C, 54.56; H, 3.17. Found: C, 54.74; H, 3.47.

*4.3.5. 2-[5-(2-Trifluoromethyl[1,3]dioxolan-2-yl)-1H-pyrazol-3-yl]phenol (**5**).* Hydrazine hydrate (0.10 mL, 1.3 mmol) was added to a solution of chromone **4** (250 mg, 0.87 mmol) in ethanol (10 mL). The solution was heated at reflux for 6 h. The cooled mixture was poured into water (10 mL) and the product was filtered and dried to give pyrazole **5** as colourless crystals in 0.20 g yield (77%), mp 136–137 °C. IR (ATR): 3401, 1596, 1558, 1472 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ (**A-5**, 70%) 4.14–4.32 (m, 4H, $2CH_2$), 6.81 (br s, 1 H, H-4′), 6.88 (td, *J* = 7.5, 1.1 Hz, 1H, H-4), 6.97 (br d, *J* = 7.5 Hz, 1H, H-3), 7.18 (ddd, *J* = 8.3, 7.2, 1.6 Hz, 1H, H-5), 7.63 (d, *J* = 6.9 Hz, 1H, H-6), 10.25 (br s, 1H, NH), 13.09 (br s, 1H, OH); (**B-5**, 30%) 4.14–4.32 (m, 4H, $2CH_2$), 6.88 (td, *J* = 7.5, 1.1 Hz, 1H, H-4), 6.90–7.00 (br s, 1H, H-4′), 7.04 (br s, 1H, H-3), 7.18 (ddd, *J* = 8.3, 7.2, 1.6 Hz, 1H, H-5), 7.81 (br s, 1H, H-6), 10.49 (br s, 1H, OH), 13.70 (br s, 1H, NH); ^{19}F NMR (376 MHz, DMSO-d_6) δ (**A-5**, 70%) 82.8 (s, CF_3), (**B-5**, 30%) 81.3 (s, CF_3). Anal. Calcd for $C_{13}H_{11}F_3N_2O_3$: C, 52.01; H, 3.69; N, 9.33. Found: C, 52.02; H, 3.62; N, 9.35.

4.4. General procedure for the synthesis of compounds 6a–c

A solution of the corresponding chromone **2** (1.0 mmol), ethylenediamine (87 mg, 1.45 mmol) and AcOH (174 mg, 2.90 mmol) in methanol (4 mL) was kept for 48 h at room temperature. After partial evaporation of the solvent and cooling the product was filtered and recrystallized from methanol to give compounds **6** as orange crystals.

*4.4.1. (Z)-1-(2-Hydroxyphenyl)-2-(3-trifluoromethyl-5,6-dihydropyrazin-2(1H)-ylidene)ethanone (**6a**).* Yield 57%, mp 183 °C. IR (ATR): 3249, 2984, 2856, 1590, 1574, 1549, 1523, 1481 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.38 (td, *J* = 6.6, 3.5 Hz, 2H, CH_2-6), 4.06 (t, *J* = 6.6 Hz, 2H, CH_2-5), 6.21 (q, $^5J_{H,F}$ = 1.5 Hz, 1H, =CH), 6.92 (dd, *J* = 8.2, 1.1 Hz, 1H, H-3′), 6.93 (td, *J* = 7.6, 1.1 Hz, 1H, H-5′), 7.43 (ddd, *J* = 8.2, 7.3, 1.6 Hz, 1H, H-4′), 7.66 (dd, *J* = 8.0, 1.6 Hz, 1H, H-6′), 10.49 (t, *J* = 3.5 Hz, 1H, NH), 12.46 (s, 1H, OH); ^{19}F NMR (376 MHz, DMSO-d_6) δ 97.2 (br s, CF_3). Anal. Calcd for $C_{13}H_{11}F_3N_2O_2$: C, 54.93; H, 3.90; N, 9.86. Found: C, 54.82; H, 3.76; N, 9.82.

*4.4.2. (Z)-1-(2-Hydroxy-5-methylphenyl)-2-(3-trifluoromethyl-5,6-dihydropyrazin-2(1H)-ylidene)ethanone (**6b**).* Yield 61%, mp 163–164 °C. IR (ATR): 2963, 2855, 2361, 1578, 1541, 1483 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.29 (s, 3H, Me), 3.40 (td, *J* = 6.4, 3.5 Hz, 2H, CH_2-6), 4.04 (t, *J* = 6.4 Hz, 2H, CH_2-5), 6.13 (s, 1H, =CH), 6.75 (d, *J* = 8.4 Hz, 1H, H-3′), 7.18 (dd, *J* = 8.4,

1.8 Hz, 1H, H-4′), 7.33 (d, *J* = 1.8 Hz, 1H, H-6′), 10.44 (br s, 1H, NH), 12.44 (s, 1H, OH); ^{19}F NMR (376 MHz, DMSO-d_6) δ 97.2 (s, CF_3). Anal. Calcd for $C_{14}H_{13}F_3N_2O_2 \cdot 0.2H_2O$: C, 55.70; H, 4.47; N, 9.28. Found: C, 55.77; H, 4.23; N, 9.01.

*4.4.3. (Z)-1-(5-Chloro-2-hydroxyphenyl)-2-(3-trifluoromethyl-5,6-dihydropyrazin-2(1H)-ylidene)ethanone (**6c**).* Yield 48%, mp 179–180 °C. IR (ATR): 3224, 2956, 1594, 1568, 1541, 1518, 1467 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.39 (td, *J* = 6.4, 3.5 Hz, 2H, CH_2-6), 4.04 (t, *J* = 6.4 Hz, 2H, CH_2-5), 6.22 (s, 1H, =CH), 6.92 (d, *J* = 8.8 Hz, 1H, H-3′), 7.37 (dd, *J* = 8.8, 2.7 Hz, 1H, H-4′), 7.54 (d, *J* = 2.7 Hz, 1H, H-6′), 10.54 (s, 1H, NH), 12.03 (br s, 1H, OH); ^{19}F NMR (376 MHz, DMSO-d_6) δ 97.3 (s, CF_3); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.41 (td, *J* = 6.3, 3.4 Hz, 2H, CH_2-6), 4.11 (t, *J* = 6.3 Hz, 2H, CH_2-5), 6.16 (q, $^5J_{H,F}$ = 1.2 Hz, 1H, =CH), 6.91 (d, *J* = 8.8 Hz, 1H, H-3′), 7.34 (dd, *J* = 8.8, 2.5 Hz, 1H, H-4′), 7.55 (d, *J* = 2.5 Hz, 1H, H-6′), 10.53 (br s, 1H, NH), 12.70 (s, 1H, OH); ^{19}F NMR (470.5 MHz, $CDCl_3$) δ 95.2 (q, $^5J_{F,H}$ = 1.5 Hz, CF_3); ^{13}C (126 MHz, $CDCl_3$): 35.3 (C-6), 47.9 (C-5), 89.5 (q, $^4J_{C,F}$ = 3.8 Hz, =CH), 119.0 (q, $^1J_{C,F}$ = 277.6 Hz, CF_3), 120.0 (C-3′), 121.1 (C-1′), 123.5 (C-5′), 127.3 (C-6′), 134.8 (C-4′), 153.1 (q, $^2J_{C,F}$ = 34.9 Hz, C-3), 160.8 (C-2′), 193.7 (C=O). Anal. Calcd for $C_{13}H_{10}ClF_3N_2O_2$: C, 49.00; H, 3.16; N, 8.79. Found: C, 49.01; H, 3.09; N, 8.75.

4.5. General procedure for the synthesis of compounds 7a–c

A solution of the corresponding chromone **2** (1.2 mmol) and *o*-phenylenediamine (160 mg, 1.5 mmol) in AcOH (5 mL) was heated at reflux for 4 h and allowed to stand at room temperature overnight. The solid that formed was filtered and washed with cooled ethanol to give compounds **7** as red or orange crystals.

*4.5.1. (Z)-1-(2-Hydroxyphenyl)-2-(3-trifluoromethylquinoxalin-2(1H)-ylidene)ethanone (**A-7a**) and (Z)-1-(2-hydroxyphenyl)-2-(3-trifluoromethylquinoxalin-2-yl)ethanone (**B-7a**).* Yield 83%, red crystals, mp 175 °C. IR (ATR): 3054, 1601, 1577, 1544, 1499, 1483 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ (**A**, 40%) 6.94–7.04 (m, 3H, H-3′, H-5′, =CH), 7.38 (ddd, *J* = 8.4, 7.0, 1.5 Hz, 1H, H-4′), 7.65 (ddd, *J* = 8.0, 7.2, 1.0 Hz, 1H, H-6), 7.83 (dd, *J* = 7.7, 1.6 Hz, 1H, H-6′), 7.88 (ddd, *J* = 8.3, 7.2, 1.2 Hz, 1H, H-7), 8.00 (m, 1H, H-8), 8.04 (dd, *J* = 8.0, 1.5 Hz, 1H, H-5), 11.53 (br s, 1H, OH), 15.16 (br s, 1H, NH); (**B**, 60%) 5.07 (q, ^5J = 1.5 Hz, 2H, CH_2), 6.97–7.04 (m, 2H, H-3′, H-5′), 7.55 (ddd, *J* = 8.5, 7.0, 1.7 Hz, 1H, H-4′), 7.92 (dd, *J* = 8.0, 1.6 Hz, 1H, H-6′), 8.00 (m, 2H, H-6), 8.07 (ddd, *J* = 8.4, 7.0, 1.6 Hz, 1H, H-7), 8.18 (dd, *J* = 8.4, 1.5 Hz, 1H, H-8), 8.29 (dd, *J* = 8.2, 1.3 Hz, 1H, H-5), 11.19 (br s, 1H, OH); ^{19}F NMR (470.5 MHz, DMSO-d_6) δ (**A**, 40%) 96.1 (d, $^5J_{F,H}$ = 1.9 Hz, CF_3); (**B**, 60%) 98.8 (t, $^5J_{F,H}$ = 1.5 Hz, CF_3); ^{1}H NMR (400 MHz, $CDCl_3$) δ (**A**, 42%) 6.48 (q,

$^{5}J_{H,F}$ = 1.7 Hz, 1H, =CH), 6.91 (ddd, 1H, H-5′, *J* = 8.2, 7.0, 1.2 Hz), 6.98 (dd, *J* = 8.2, 1.2 Hz, 1H, H-3′), 7.37–7.44 (m, 3H, H-6, H-7, H-8), 7.66 (ddd, *J* = 8.5, 7.2, 1.5 Hz, 1H, H-4′), 7.71 (dd, *J* = 8.0, 1.5 Hz, 1H, H-6′), 7.84–7.94 (m, 1H, H-5), 12.66 (s, 1H, OH), 15.12 (br s, 1H, NH); (**B**, 58%) 4.97 (q, $^{5}J_{H,F}$ = 1.3 Hz, 2H, CH_2), 6.98 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H, H-5′), 7.03 (dd, 1H, H-3′, *J* = 8.4, 1.0 Hz), 7.54 (ddd, *J* = 8.5, 7.2, 1.5 Hz, 1H, H-4′), 7.84–7.94 (m, 3H, H-6′, H-6, H-7), 8.13 (dd, *J* = 7.8, 1.8 Hz, 1H, H-8), 8.25 (dd, *J* = 7.8, 1.8 Hz, 1H, H-5), 11.76 (s, 1H, OH); ^{19}F NMR ($CDCl_3$) δ (**A**, 42%) 94.3 (s, CF_3); (**B**, 58%) 98.0 (s, CF_3); ^{13}C NMR (126 MHz, DMSO-d_6) δ (**A**) 90.9 (q, $^{4}J_{C,F}$ = 3.4 Hz, =CH), 117.3 (C-3′), 119.2 (C-5′), 120.6 (q, $^{1}J_{C,F}$ =275.8 Hz, CF_3), 121.0 (C-1′), 121.3 (C-8), 127.4 (C-6), 128.3 (C-6′), 129.6 (C-5), 133.0 (C-4′), 134.0 (C-7), 134.4 (C-4a), 134.6 (C-8a), 141.0 (q, $^{2}J_{C,F}$ = 34.4 Hz, C-3), 145.2 (C-2), 158.3 (C-2′), 178.2 (C=O), (**B**) 48.2 (q, $^{4}J_{C,F}$ = 2.0 Hz, CH_2), 117.6 (C-3′), 119.4 (C-5′), 121.3 (q, $^{1}J_{C,F}$ = 276.0 Hz, CF_3), 121.5 (C-1′), 128.5 (C-8), 129.3 (C-5), 130.5 (C-6′), 131.6 (C-6), 133.2 (C-7), 135.9 (C-4′), 138.5 (C-4a), 141.0 (q, $^{2}J_{C,F}$ = 33.7 Hz, C-3), 142.2 (C-8a), 148.7 (C-2), 159.6 (C-2′), 199.0 (C=O). Anal. Calcd for $C_{17}H_{11}F_3N_2O_2$: C, 61.45; H, 3.34; N, 8.43. Found: C, 61.27; H, 3.37; N, 8.41.

*4.5.2. (Z)-1-(2-Hydroxy-5-methylphenyl)-2-(3-trifluoromethylquinoxalin-2(1H)-ylidene)ethanone (**A-7b**) and 1-(2-hydroxy-5-methylphenyl)-2-(3-trifluoromethylquinoxalin-2-yl)ethanone (**B-7b**).* Yield 79%, red crystals, mp 211–212 °C. IR (ATR): 1615, 1601, 1582, 1541, 1481 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ (**A**, 42%) 2.32 (s, 3H, Me), 6.76 (q, $^{5}J_{H,F}$ = 1.7 Hz, 1H, =CH), 6.80 (d, *J* = 8.4 Hz, 1H, H-3′), 7.14 (dd, *J* = 8.4, 1.8 Hz, 1H, H-4′), 7.50 (d, *J* = 1.8 Hz, 1H, H-6′), 7.55 (ddd, *J* = 7.9, 7.0, 1.3 Hz, 1H, H-6/7), 7.79 (td, *J* = 7.6, 1.0 Hz, 1H, H-7/6), 7.92 (d, *J* = 7.9 Hz, 1H, H-8), 8.00 (d, *J* = 7.9 Hz, 1H, H-5), 11.49 (s, 1H, OH), 15.09 (s, 1H, NH); (**B**, 58%) 2.34 (s, 3H, Me), 5.01 (q, $^{5}J_{H,F}$ = 1.4 Hz, 2H, CH_2), 6.87 (d, *J* = 8.3 Hz, 1H, H-3′), 7.31 (dd, *J* = 8.4, 1.9 Hz, 1H, H-4′), 7.76 (d, *J* = 1.8 Hz, 1H, H-6′), 7.83 (td, *J* = 7.5, 1.0 Hz, 1H, H-6/7), 7.96 (td, *J* = 7.5, 1.2 Hz, 1H, H-7/6), 8.13 (dd, *J* = 8.0, 1.5 Hz, 1H, H-8), 8.23 (dd, *J* = 8.0, 1.5 Hz, 1H, H-5), 11.06 (s, 1H, OH); ^{19}F NMR (376 MHz, DMSO-d_6) δ (**A**, 42%) 96.1 (d, $^{5}J_{F,H}$ = 1.7 Hz, CF_3); (**B**, 58%) 98.9 (t, $^{5}J_{F,H}$ = 1.4 Hz, CF_3). Anal. Calcd for $C_{18}H_{13}F_3N_2O_2$: C, 62.43; H, 3.78; N, 8.09. Found: C, 62.40; H, 3.79; N, 8.07.

*4.5.3. (Z)-1-(5-Chloro-2-hydroxyphenyl)-2-(3-trifluoromethylquinoxalin-2(1H)-ylidene)ethanone (**A-7c**) and 1-(5-chloro-2-hydroxyphenyl)-2-(3-trifluoromethylquinoxalin-2-yl)ethanone (**B-7c**).* Yield 87%, orange crystals, mp 187–188 °C. IR (ATR): 3056, 1613, 1603, 1569, 1548, 1481, 1470 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ (**A**, 58%) 6.95 (d, *J* = 8.7 Hz, 1H, H-3′), 7.05 (d, $^{5}J_{H,F}$ = 1.6 Hz, 1H, =CH), 7.28 (dd, *J* = 8.7, 2.7 Hz, 1H, H-4′), 7.66 (ddd, *J* = 8.2, 7.0, 1.1 Hz, 1H, H-7), 7.73 (d, *J* = 2.7 Hz, 1H, H-6′), 7.84 (d, *J* = 2.7 Hz, 1H, H-6), 7.94 (d, *J* = 8.4 Hz, 1H, H-8), 7.95–8.05

(m, 1H, H-5), 11.30 (br s, 1H, OH), 15.28 (br s, 1H, NH); (**B**, 42%) 4.99 (q, $^{5}J_{H,F}$ = 1.4 Hz, 2H, CH_2), 7.02 (d, *J* = 8.8 Hz, 1H, H-3′), 7.45 (dd, *J* = 8.9, 2.7 Hz, 1H, H-4′), 7.86 (ddd, *J* = 8.1, 7.2, 1.0 Hz, 1H, H-7), 7.95–8.05 (m, 2H, H-6′, H-6), 8.12 (dd, *J* = 8.0, 1.4 Hz, 1H, H-8), 8.23 (dd, *J* = 7.8, 1.5 Hz, 1H, H-5), 11.30 (br s, 1H, OH); ^{19}F NMR (376 MHz, DMSO-d_6) δ (**A**, 58%) 96.4 (d, $^{5}J_{F,H}$ = 1.6 Hz, CF_3); (**B**, 42%) 98.8 (t, $^{5}J_{F,H}$ = 1.4 Hz, CF_3). Anal. Calcd for $C_{17}H_{10}ClF_3N_2O_2$: C, 55.68; H, 2.75; N, 7.64. Found: C, 55.31; H, 2.68; N, 7.60.

4.6. General procedure for the synthesis of compounds 8a–c

A solution of the corresponding chromone **2** (1.0 mmol) and 2,3-diaminonaphthaline (190 mg, 1.2 mmol) in AcOH (5 mL) was heated at reflux for 4 h and allowed to stand at room temperature overnight. The solid that formed was filtered and washed with cooled ethanol to give compounds **8** as maroon crystals.

*4.6.1. (Z)-1-(2-Hydroxyphenyl)-2-(3-trifluoromethylbenzo[g]quinoxalin-2(1H)-ylidene)ethanone (**8a**)*. Yield 88%, mp 262–263 °C. IR (KBr): 1609, 1579, 1551, 1485 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.56 (q, $^{5}J_{H,F}$ = 1.6 Hz, 1H, =CH), 6.93 (ddd, *J* = 8.1, 7.1, 1.0 Hz, 1H, H-5′), 7.00 (dd, *J* = 8.4, 1.0 Hz, 1H, H-3′), 7.44 (ddd, *J* = 8.4, 7.1, 1.5 Hz, 1H, H-4′), 7.50 (ddd, *J* = 8.3, 6.9, 1.2 Hz, 1H, H-7), 7.62 (ddd, *J* = 8.2, 6.9, 1.3 Hz, 1H, H-8), 7.70 (s, 1H, H-10), 7.74 (dd, *J* = 8.1, 1.5 Hz, 1H, H-6′), 7.88 (d, *J* = 8.2 Hz, 1H, H-9), 7.97 (d, *J* = 8.3 Hz, 1H, H-6), 8.41 (s, 1H, H-5), 12.77 (s, 1H, OH), 14.46 (br s, 1H, NH); ^{19}F NMR (470.5 MHz, $CDCl_3$) δ 93.8 (d, $^{5}J_{F,H}$ = 1.6 Hz, CF_3); ^{13}C NMR (126 MHz, $CDCl_3$): δ 89.2 (q, $^{4}J_{C,F}$ = 3.7 Hz, =CH), 112.1 (C-10), 118.6 (C-3′), 119.0 (C-5′), 120.1 (q, $^{1}J_{C,F}$ = 276.1 Hz, CF_3), 121.5 (C-1′), 125.9 (C-7), 126.9 (C-9), 127.3 (C-10a), 128.2 (C-6′), 129.2 (C-6), 129.5 (C-8), 130.6 (C-5),130.9 (C-5a),132.0 (C-4a), 135.1 (C-4′), 136.0 (C-9a), 140.2 (C-2), 144.9 (q, $^{2}J_{C,F}$ = 35.3 Hz, C-3), 162.3 (C-2′), 193.3 (C=O). Anal. Calcd for $C_{21}H_{13}F_3N_2O_2$: C, 65.97; H, 3.43; N, 7.33. Found: C, 65.77; H, 3.42; N, 7.24.

*4.6.2. (Z)-1-(2-Hydroxy-5-methylphenyl)-2-(3-trifluoromethylbenzo[g]quinoxalin-2(1H)-ylidene)ethanone (**8b**)*. Yield 80%, mp 283 °C. IR (KBr): 1611, 1585, 1551, 1491, 1470 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.36 (s, 3H, Me), 6.54 (q, $^{5}J_{H,F}$ = 1.3 Hz, 1H, =CH), 6.91 (d, *J* = 8.5 Hz, 1H, H-3′), 7.25 (d, *J* = 8.5 Hz, 1H, H-4′), 7.48 (s, 1H, H-6′), 7.50 (ddd, *J* = 8.2, 7.0, 1.0 Hz, 1H, H-7), 7.62 (ddd, *J* = 8.2, 7.0, 1.0 Hz, 1H, H-8), 7.70 (s, 1H, H-10), 7.88 (d, *J* = 8.2 Hz, 1H, H-9), 7.97 (d, *J* = 8.2 Hz, 1H, H-6), 8.41 (s, 1H, H-5), 12.59 (s, 1H, OH), 14.50 (s, 1H, NH); ^{19}F NMR (376 MHz, $CDCl_3$) δ 95.0 (s, CF_3). Anal. Calcd for $C_{22}H_{15}F_3N_2O_2$: C, 66.67; H, 3.81; N, 7.07. Found: C, 66.34; H, 3.71; N, 7.06.

*4.6.3. (Z)-1-(5-Chloro-2-hydroxyphenyl)-2-(3-trifluoromethylbenzo[g]quinoxalin-2(1H)-ylidene)ethanone (**8c**).* Yield 98%, mp 269–270 °C. IR (KBr): 1610, 1577, 1550, 1467 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.46 (q, $^5J_{H,F}$ = 1.5 Hz, 1H, =CH), 6.96 (d, *J* = 8.8 Hz, 1H, H-3′), 7.38 (dd, *J* = 8.8, 2.5 Hz, 1H, H-4′), 7.52 (ddd, *J* = 8.2, 6.9, 1.1 Hz, 1H, H-7), 7.64 (ddd, *J* = 8.2, 6.9, 1.1 Hz, 1H, H-8), 7.65 (d, *J* = 2.5 Hz, 1H, H-6′), 7.75 (s, 1H, H-10), 7.90 (d, *J* = 8.2 Hz, 1H, H-9), 8.00 (d, *J* = 8.2 Hz, 1H, H-6), 8.46 (s, 1H, H-5), 12.72 (s, 1H, OH), 14.60 (s, 1H, NH); ^{19}F NMR (376 MHz, $CDCl_3$) δ 95.2 (s, CF_3). Anal. Calcd for $C_{21}H_{12}ClF_3N_2O_2$: C, 60.52; H, 2.90; N, 6.72. Found: C, 60.24; H, 2.78; N, 6.69.

4.7. General procedures for the synthesis of compounds 9a–c and 10a–c

Method *A*. A solution of the corresponding chromone **2** (1.0 mmol) and 2,3-diaminopyridine (131 mg, 1.2 mmol) in AcOH (5 mL) was heated at reflux for 4 h and allowed to stand at room temperature overnight. The solid that formed was filtered and washed with cooled ethanol to give a mixture of compounds **9** and **10** as orange or red crystals.

Method *B*. A solution of the corresponding chromone **2** (0.5 mmol) and 2,3-diaminopyridine (66 mg, 0.6 mmol) in AcOH (3 mL) was allowed to stand at room temperature during one week. The solid that formed was filtered and washed with ethanol to give a mixture of enamine **A-9** and imine **B-9**. From the mother liquor additional amounts of forms **A-9**, **B-9**, and **A-10** were isolated and washed with ethanol (Table 3).

*4.7.1. (Z)-1-(2-Hydroxyphenyl)-2-(3-trifluoromethylpyrido[2,3-b]pyrazin-2(1H)-ylidene)ethanone (**9a**) and (Z)-1-(2-hydroxyphenyl)-2-(2-trifluoromethylpyrido[2,3-b]pyrazin-3(4H)-ylidene)ethanone (**10a**).* Yield 88%, light red crystals, mp 209–210 °C (method *A*); yield 85%, mp 210–213 °C (method *B*). IR (KBr): 1617, 1583, 1556, 1491, 1438 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ (**A-9a**, 9%) 6.58 (q, $^5J_{H,F}$ = 1.7 Hz, 1H, =CH), 6.92 (m, 1H, H-5′), 6.99 (dd, *J* = 8.3, 1.2 Hz, 1H, H-3′), 7.44 (ddd, *J* = 8.3, 7.0, 1.6 Hz, 1H, H-4′), 7.59 (dd, *J* = 8.3, 4.4 Hz, 1H, H-7), 7.71 (m, 1H, H-6′), 7.74 (dd, *J* = 8.3, 1.6 Hz, 1H, H-8), 8.70 (dd, *J* = 4.4, 1.6 Hz, 1H, H-6), 12.37 (s, 1H, OH), 14.96 (s, 1H, NH); (**B-9a**, 31%) 5.02 (q, $^5J_{H,F}$ = 1.2 Hz, 2H, CH_2), 6.99 (ddd, *J* = 8.1, 7.1, 1.1 Hz, 1H, H-5′), 7.04 (dd, *J* = 8.5, 1.1 Hz, 1H, H-3′), 7.55 (ddd, *J* = 8.3, 7.2, 1.5 Hz, 1H, H-4′), 7.85 (dd, *J* = 7.9, 1.5 Hz, 1H, H-6′), 7.87 (dd, *J* = 8.4, 4.1 Hz, 1H, H-7), 8.50 (dd, *J* = 8.4, 1.9 Hz, 1H, H-8), 9.31 (dd, *J* = 4.1, 1.9 Hz, 1H, H-6), 11.69 (s, 1H, OH); (**A-10a**, 56%) 6.53 (q, $^5J_{H,F}$ = 1.7 Hz, 1H, =CH), 6.92 (m, 1H, H-5′), 6.99 (dd, *J* = 8.3, 1.2 Hz, 1H, H-3′), 7.31 (dd, *J* = 8.0, 4.7 Hz, 1H, H-7), 7.44 (ddd, *J* = 8.3, 7.0, 1.6 Hz, 1H, H-4′), 7.71 (dd, *J* = 8.1, 1.6 Hz, 1H, H-6′), 8.10 (dd, *J* = 8.0, 1.7 Hz, 1H, H-8), 8.60 (dd, *J* = 4.7, 1.7 Hz, 1H, H-6), 12.66 (s, 1H, OH), 14.36 (s, 1H, NH); (**B-10a**, 4%) 5.08 (q, $^5J_{H,F}$ = 1.4 Hz, 2H, CH_2), 6.99 (dd, *J* = 8.3, 1.2 Hz, 1H, H-3′), 7.02 (m, 1H, H-5′), 7.55

(ddd, *J* = 8.3, 7.2, 1.6 Hz, 1H, H-4′), 7.86 (dd, *J* = 8.6, 4.0 Hz, 1H, H-7), 7.88 (dd, *J* = 9.2, 1.3 Hz, 1H, H-6′), 8.63 (dd, *J* = 8.6, 1.9 Hz, 1H, H-8), 9.32 (dd, *J* = 4.0, 1.9 Hz, 1H, H-6), 11.65 (s, 1H, OH); ^{19}F NMR (470.5 MHz, $CDCl_3$) δ(**A-9a**, 9%) 92.8 (d, $^5J_{F,H}$ = 1.7 Hz, CF_3); (**B-9a**, 31%) 96.5 (t, $^5J_{F,H}$ = 1.2 Hz, CF_3); (**A-10a**, 56%) 92.9 (d, $^5J_{F,H}$ = 1.7 Hz, CF_3); (**B-10a**, 4%) 97.0 (t, $^5J_{F,H}$ = 1.4 Hz, CF_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ(**A-9a**) 89.1 (q, $^2J_{C,F}$ = 3.4 Hz, =CH), 118.7 (C-3′), 118.9 (C-5′), 120.0 (C-1′), 125.1 (C-8), 127.7 (C-8a), 128.16 (C-7/C-6′), 128.19 (C-6′/C-7), 135.4 (C-4′), 141.0 (C-2), 143.9 (C-4a), 147.9 (C-6), 162.1 (C-2′), 192.3 (C=O), CF_3 and C-3 were not found; (**B-9a**) 45.0 (q, $^4J_{C,F}$ = 2.3 Hz, CH_2), 118.9 (C-3′), 119.4 (C-5′), 120.0 (C-1′), 120.9 (q, $^1J_{C,F}$ = 276.7 Hz, CF_3), 127.5 (C-7), 129.8 (C-6′), 137.1 (C-4′), 138.0 (C-8), 138.7 (q, $^5J_{C,F}$ = 0.9 Hz, C-8a), 144.6 (q, $^2J_{C,F}$ = 35.4 Hz, C-3), 148.0 (q, $^4J_{C,F}$ = 1.0 Hz, C-4a), 149.3 (C-2), 155.8 (C-6), 162.7 (C-2′), 200.6 (C=O); (**A-10a**) 89.2 (q, $^4J_{C,F}$ = 3.5 Hz, =CH), 118.8 (C-3′), 119.0 (C-5′), 119.8 (q, $^1J_{C,F}$ = 276.6 Hz, CF_3), 120.3 (C-1′), 121.1 (C-7), 128.1 (q, $^4J_{C,F}$ = 0.9 Hz, C-8a), 128.2 (C-6′), 135.4 (C-4′), 137.9 (C-8), 141.2 (C-3), 142.4 (C-4a), 145.4 (q, $^2J_{C,F}$ = 35.6 Hz, C-2), 154.1 (C-6), 162.6 (C-2′), 193.6 (C=O); (**B-10a**) 45.6 (q, $^4J_{C,F}$ = 2.0 Hz, CH_2), 118.9 (C-3′), 119.2 (C-5′), 120.0 (C-1′), 126.6 (C-7), 129.8 (C-6′), 137.1 (C-4′), 138.9 (C-8), 151.4 (C-3), 156.9 (C-6), 162.6 (C-2′), 200.5 (C=O), CF_3, C-8a, C-4a and C-2 were not found. Anal. Calcd for $C_{16}H_{10}F_3N_3O_2$: C, 57.66; H, 3.02; N, 12.61. Found: C, 57.54; H, 3.01; N, 12.57.

*4.7.2. (Z)-1-(2-Hydroxy-5-methylphenyl)-2-(3-trifluoromethylpyrido[2,3-b]pyrazin-2(1H)-ylidene)ethanone (**9b**) and (Z)-1-(2-hydroxy-5-methylphenyl)-2-(2-trifluoromethylpyrido[2,3-b]pyrazin-3(4H)-ylidene)ethanone (**10b**).* Yield 91%, orange crystals, mp 202–203 °C (method *A*); yield 89%, mp 206–209 °C (method *B*). IR (KBr): 1615, 1577, 1551, 1541, 1491 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ(**A-9b**, 14%) 2.35 (s, 3H, Me), 6.56 (q, $^5J_{H,F}$ = 1.7 Hz, 1H, =CH), 6.89 (d, *J* = 8.4 Hz, 1H, H-3′), 7.25 (dd, *J* = 8.4, 2.0 Hz, 1H, H-4′), 7.45 (d, *J* = 2.0 Hz, 1H, H-6′), 7.58 (dd, *J* = 8.2, 4.4 Hz, 1H, H-7), 7.74 (dd, *J* = 8.2, 1.6 Hz, 1H, H-8), 8.69 (dd, *J* = 4.4, 1.6 Hz, 1H, H-6), 12.18 (s, 1H, OH), 15.01 (s, 1H, NH); (**B-9b**, 64%) 2.37 (s, 3H, Me), 5.01 (q, $^5J_{H,F}$ = 1.3 Hz, 2H, CH_2), 6.95 (d, *J* = 8.5 Hz, 1H, H-3′), 7.37 (dd, *J* = 8.5, 2.0 Hz, 1H, H-4′), 7.62 (d, *J* = 2.0 Hz, 1H, H-6′), 7.87 (dd, *J* = 8.4, 4.1 Hz, 1H, H-7), 8.50 (dd, *J* = 8.4, 1.9 Hz, 1H, H-8), 9.31 (dd, *J* = 4.1, 1.9 Hz, 1H, H-6), 11.52 (s, 1H, OH); (**A-10b**, 20%) 2.35 (s, 3H, Me), 6.51 (q, $^5J_{H,F}$ = 1.7 Hz, 1H, =CH), 6.90 (d, *J* = 8.4 Hz, 1H, H-3′), 7.25 (dd, *J* = 8.4, 2.0 Hz, 1H, H-4′), 7.31 (dd, *J* = 8.0, 4.7 Hz, 1H, H-7), 7.45 (d, *J* = 2.0 Hz, 1H, H-6′), 8.10 (dd, *J* = 8.0, 1.8 Hz, 1H, H-8), 8.59 (dd, *J* = 4.7, 1.8 Hz, 1H, H-6), 12.48 (s, 1H, OH), 14.39 (s, 1H, NH); (**B-10b**, 2%) 2.38 (s, 3H, Me), 5.06 (q, $^5J_{H,F}$ = 1.3 Hz, 2H, CH_2), 6.94 (d, *J* = 8.6 Hz, 1H, H-3′), 7.25 (dd, *J* = 8.4, 2.0 Hz, 1H, H-4′), 7.45 (d, *J* = 2.0 Hz, 1H, H-6′), 7.87 (dd, *J* = 8.4, 4.2 Hz, 1H, H-7), 8.63 (dd, *J* = 8.4, 1.9 Hz, 1H, H-8), 9.31 (dd, *J* = 4.2, 1.9 Hz, 1H, H-6), 11.48 (s, 1H, OH); ^{19}F NMR (470.5 MHz, $CDCl_3$) δ(**A-9b**, 14%) 92.8 (d, $^5J_{F,H}$ =

1.7 Hz, CF_3); (**B-9b**, 64%) 96.6 (t, $^5J_{F,H}$ = 1.3 Hz, CF_3); (**A-10b**, 20%) 93.0 (d, $^5J_{F,H}$ = 1.7 Hz, CF_3); (**B-10b**, 2%) 97.0 (t, $^5J_{F,H}$ = 1.3 Hz, CF_3). Anal. Calcd for $C_{17}H_{12}F_3N_3O_2$: C, 58.79; H, 3.48; N, 12.10. Found: C, 58.69; H, 3.59; N, 11.99.

*4.7.3. (Z)-1-(5-Chloro-2-hydroxyphenyl)-2-(3-trifluoromethylpyrido[2,3-b]pyrazin-2(1H)-ylidene)ethanone (**9c**) and (Z)-1-(5-chloro-2-hydroxyphenyl)-2-(2-trifluoromethylpyrido[2,3-b]pyrazin-3(4H)-ylidene)ethanone (**10c**).* Yield 98%, red crystals, mp 256–257 °C (method *A*); yield 95%, mp 250–253 °C (method *B*). IR (KBr): 1618, 1580, 1551, 1479, 1462 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ (**A-9c**, 25%) 6.50 (q, $^5J_{H,F}$ = 1.6 Hz, 1H, =CH), 6.96 (d, *J* = 8.8 Hz, 1H, H-3′), 7.39 (dd, *J* = 8.8, 2.5 Hz, 1H, H-4′), 7.62 (dd, *J* = 8.2, 4.4 Hz, 1H, H-7), 7.63 (d, *J* = 2.5 Hz, 1H, H-6′), 7.79 (dd, *J* = 8.2, 1.6 Hz, 1H, H-8), 8.75 (dd, *J* = 4.4, 1.6 Hz, 1H, H-6), 12.32 (s, 1H, OH), 15.11 (s, 1H, NH); (**B-9c**, 60%) 4.98 (q, $^5J_{H,F}$ = 1.3 Hz, 2H, CH_2), 7.02 (d, *J* = 9.0 Hz, 1H, H-3′), 7.51 (dd, *J* = 9.0, 2.6 Hz, 1H, H-4′), 7.82 (d, *J* = 2.6 Hz, 1H, H-6′), 7.88 (dd, *J* = 8.5, 4.1 Hz, 1H, H-7), 8.50 (dd, *J* = 8.5, 1.9 Hz, 1H, H-8), 9.33 (dd, *J* = 4.1, 1.9 Hz, 1H, H-6), 11.60 (s, 1H, OH); (**A-10c**, 15%) 6.43 (q, $^5J_{H,F}$ = 1.7 Hz, 1H, =CH), 6.96 (d, *J* = 8.8 Hz, 1H, H-3′), 7.36 (dd, *J* = 8.0, 4.7 Hz, 1H, H-7), 7.39 (dd, *J* = 8.8, 2.5 Hz, 1H, H-4′), 7.64 (d, *J* = 2.5 Hz, 1H, H-6′), 8.15 (dd, *J* = 8.0, 1.7 Hz, 1H, H-8), 8.64 (dd, *J* = 4.7, 1.7 Hz, 1H, H-6), 12.62 (s, 1H, OH), 14.47 (s, 1H, NH); ^{19}F NMR (470.5 MHz, $CDCl_3$) δ (**A-9c**, 25%) 93.0 (d, $^5J_{F,H}$ = 1.7 Hz, CF_3); (**B-9c**, 60%) 96.6 (t, $^5J_{F,H}$ = 1.3 Hz, CF_3); (**A-10c**, 15%) 93.1 (d, $^5J_{F,H}$ = 1.7 Hz, CF_3). Anal. Calcd for $C_{16}H_9ClF_3N_3O_2$: C, 52.26; H, 2.47; N, 11.43. Found: C, 52.11; H, 2.43; N, 11.43.

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References and notes

1. (a) Cheeseman, G. W. H.; Cookson, R. F. *Condensed Pyrazines*, in: *Heterocyclic Compounds* (Eds.: Weissberger, A.; Taylor, E. C.); Wiley: New York, 1979, vol. 35, pp 78–94; (b) Sanna, P.; Carta, A.; Loriga, M.; Zanetti, S.; Sechi, L. *Farmaco* **1998**, *53*, 455; (c) Sanna, P.; Carta, A.; Loriga, M.; Zanetti, S.; Sechi, L. *Farmaco* **1999**, *54*, 161; (d) Saifina, D. F.; Mamedov, V. A. *Russ. Chem. Rev*. **2010**, *79*, 351.
2. (a) Patel, M.; McHugh, R. J. Jr.; Cordova, B. C.; Klabe, R. M.; Erickson-Viitanen, S.; Trainor, G. L.; Rodgers, J. D. *Bioorg. Med. Chem. Lett*. **2000**, *10*, 1729; (b) Smits, R. A.; Lim, H. D.;

Hanzer, A.; Zuiderveld, O. P.; Guaita, E.; Adami, M.; Coruzzi, G.; Leurs, R.; de Esch, I. J. P. *J. Med. Chem*. **2008**, *51*, 2457; (c) Bahekar, R. H.; Jain, M. R.; Gupta, A. A.; Goel, A.; Jadav, P. A.; Patel, D. N.; Prajapati, V. M.; Patel, P. R. *Arch. Pharm. Chem. Life Sci*. **2007**, *340*, 359.

3. (a) Volochnyuk, D. M.; Grygorenko, O. O.; Gorlova, A. O. *Fluorine Containing Diazines. Synthesis and Properties*, in: *Fluorine in Heterocyclic Chemistry* (Ed.: Nenajdenko, V.); Springer: 2014, vol. 2, pp. 291–575; (b) Moore, L. O.; Clark, J. W. *J. Org. Chem.* **1965**, *30*, 2472; (c) Cushman, M.; Wong, W. C.; Bacher, A. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1043; (d) Kamitori, Y. *Tetrahedron Lett.* **2000**, *41*, 9267; (e) Kamitori, Y.; Hojo, M.; Masuda, R.; Fujitani, T.; Ohara, S.; Yokoyama, T. *J. Org. Chem.* **1988**, *53*, 129; (f) Kamitori, Y. *J. Heterocycl. Chem.* **2001**, *38*, 773; (g) Braña, M. F.; Cacho, M.; Ramos, A.; Domínguez, M. T.; Pozuelo, J. M.; Abradelo, C.; Rey-Stolle, M. F.; Yuste, M.; Carrasco, C.; Bailly, C. *Org. Biomol. Chem*. **2003**, *1*, 648; (h) Belcher, R.; Sykes, A.; Tatlow, J. C. *J. Chem. Soc*. **1957**, 2393.
4. (a) Ishikawa, N.; Sasaki, S. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 2164; (b) Saloutina, L. V.; Zapevalov, A. Y.; Saloutin, V. I.; Kodess, M. I.; Kirichenko, V. E.; Pervova, M. G.; Chupakhin, O. N. *Russ. J. Org. Chem*. **2006**, *42*, 558; (c) Laduron, F.; Janousek, Z.; Viehe, H. G. *J. Fluorine Chem*. **1995**, *73*, 83.
5. (a) Meshram, H. M.; Ramesh, P.; Kumar, G. S.; Reddy, B. C. *Tetrahedron Lett.* **2010**, *51*, 4313; (b) Kumar, B. S. P. A.; Madhav, B.; Reddy, K. H. V.; Nageswar, Y. V. D. *Tetrahedron Lett.* **2011**, *52*, 2862; (c) Burgart, Y. V.; Kuzueva, O. G.; Kodess, M. I.; Saloutin, V. I. *Russ. J. Org. Chem*. **1998**, *34*, 375.
6. Cushman, M.; Patel, H.; McKenzie, A. *J. Org. Chem*. **1988**, *53*, 5088.
7. (a) Murthy, S. N.; Madhav, B.; Nageswar, Y. V. D. *Helv. Chim. Acta* **2010**, *93*, 1216; (b) Sanna, P.; Carta, A.; Loriga, M.; Zanetti, S.; Sechi, L. *Farmaco* **1999**, *54*, 169.
8. Kamitori, Y. *Heterocycles* **2003**, *60*, 1185.
9. Irgashev, R. A.; Sosnovskikh, V. Y.; Kalinovich, N.; Kazakova, O.; Röschenthaler, G.-V. *Tetrahedron Lett.* **2009**, *50*, 4903.
10. (a) Hiyama, T. *Organofluorine Compounds. Chemistry and Application*; Springer-Verlag: Berlin, 2000; (b) *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications* (Eds.: Filler, R.; Kobayashi, Y.; Yagupolskii, L. M.); Elsevier: Amsterdam, 1993.
11. (a) Dolbier Jr., W. R. *J. Fluorine Chem.* **2005**, *126*, 157; (b) Bégué, J.-P.; Bonnet-Delpon, D. *J. Fluorine Chem.* **2006**, *127*, 992; (c) O'Hagan, D. *J. Fluorine Chem.* **2010**, *131*, 1071; (d) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320.
12. (a) Sosnovskikh, V. Y. *Fluorinated Pyrones, Chromones and Coumarins*, in: *Fluorine in Heterocyclic Chemistry* (Ed.: Nenajdenko, V.); Springer: 2014, vol. 2, pp. 211–290; (b) Sosnovskikh, V. Y.; Irgashev, R. A.; Barabanov, M. A. *Synthesis* **2006**, 2707; (c) Sosnovskikh,

V. Y.; Irgashev, R. A.; Kodess, M. I. *Tetrahedron* **2008**, *64*, 2997; (d) Sosnovskikh, V. Y.; Moshkin, V. S.; Kodess, M. I. *Tetrahedron* **2008**, *64*, 7877; (e) Sosnovskikh, V. Y.; Khalymbadzha, I. A.; Irgashev, R. A.; Slepukhin, P. A. *Tetrahedron* **2008**, *64*, 10172.

13. Sianesi, D.; Pasetti, A.; Tarli, F. *J. Org. Chem.* **1966**, *31*, 2312.
14. Dolenský, B.; Kvíčala, J.; Paleček, J.; Paleta, O. *J. Fluorine Chem.* **2002**, *115*, 67.
15. (a) Brown, R. C.; Cairns, H. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1553; (b) Bevan, P. S.; Ellis, G. P.; Wilson, H. K. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2552.
16. Chizhov D. L.; Sosnovskikh V. Y.; Pryadeina, M. V.; Burgart, Y. V.; Saloutin, V. I.; Charushin, V. N. *Synlett* **2008**, 281.
17. Anderson, B. C.; England, D. C.; Resnick, P. R. EP 0196693.
18. (a) Sosnovskikh, V. Y.; Irgashev, R. A.; Levchenko, A. A. *Tetrahedron* **2008**, *64*, 6607; (b) Lévai, A.; Silva, A. M. S.; Cavaleiro, J. A. S.; Alkorta, I.; Elguero, J.; Jekő, J. *Eur. J. Org. Chem.* **2006**, 2825.
19. Morin, C.; Beugelmans, R. *Tetrahedron* **1977**, *33*, 3183.
20. Markees, D. G. *J. Heterocycl. Chem.* **1989**, *26*, 29.
21. (a) Greenhill, J. V.; Loghmani-Khouzani, H. *Tetrahedron* **1988**, *44*, 3319; (b) Greenhill, J. V.; Loghmani-Khouzani, H.; Maitland, D. J. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2831; (c) Iwanami, Y.; Inagaki, T. *J. Heterocycl. Chem.* **1976**, *13*, 681.
22. Günter, H. *NMR Spectroscopy: An Introduction*; J. Wiley and Sons: Chichester, 1980, 436 pp.