3-(Polyfluoroacyl)chromones and Their Hetero Analogues as Valuable Substrates for Syntheses of 4-(Polyfluoroalkyl)pyrimidines

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Dedicated to Professor Yulian Volovenko on the occasion of his 55th birthday

Abstract: Reactions of 3-(polyfluoroacyl)chromones and their hetero analogues with a number of 1,3-*NCN*-dinucleophiles, such as amidines or guanidines, were studied in detail, and preparative access to a set of diverse 5-salicyloyl-4-(polyfluoroalkyl)pyrimidines was elaborated. These compounds appear to be a suitable starting substrates for the synthesis of 4-(polyfluoroalkyl)pyrimidine-5-carboxylic acids or pyrimidines containing a benzofuran-3-yl substituent in the 5-position.

Key words: chromones, thiochromones, fluorine, pyrimidine core annulation, regioselectivity, heterocycles

3-Acylchromones, and especially 3-formylchromones, which can be considered as 1,3-dicarbonyl compounds with a masked salicyloyl fragment at the 2-position, represent an important class of oxygen heterocycles. Molecules of these chromones possess three electrophilic centers, so their interaction with nucleophiles sometimes is somewhat unpredictable.[1] Previously, a number of preparative methods leading to pyrimidines have been elaborated on the basis of reactions of 3-acylchromones with various amidines and guanidines.[2]

Pyrimidines containing a polyfluoroalkyl group are well known pharmacophores that occur in numerous bioactive substrates. Fluorinated pyrimidines have been identified as potent and specific inhibitors of prostaglandin-endoperoxide synthase 2 (PTGS2; COX-2),[3a] as well as being useful in the treatment of some diseases, including neoplasms.[3b] Some representatives of the class are selective agonists of cannabinoid receptor type 2 (CB2) and can be used for treatment of inflammatory pain.[4] However, the range of preparative methods for incorporating a polyfluoroalkyl function in a pyrimidine moiety or for assembling the pyrimidine framework with a fluoroalkyl substituent remains limited.

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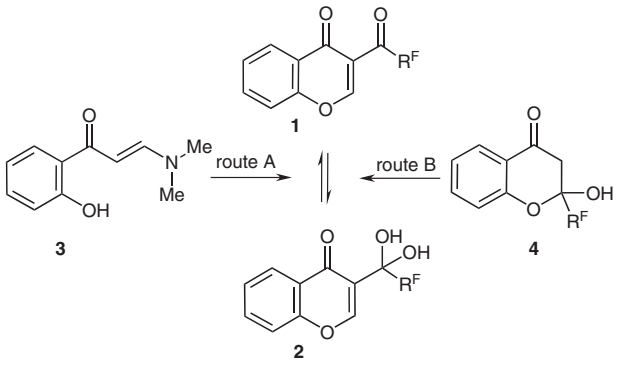
The known methods for the synthesis of fluorinated pyrimidines can be classified as belonging to one of three general strategies. The first and most commonly used approach involves a two-component reaction between a 1,3-*NCN*-dinucleophile (an amidine or guanidine) and a 1,3-*CCC*-dielectrophile bearing a fluorinated moiety.[5] The second strategy is based on the direct insertion of a fluorinated group, either from an organometallic precursor[6] or by the transformation of a specially introduced group into one containing fluorine.[7] The third general strategy involves an inverse-electron-demand Diels–Alder protocol;[8] this is comparatively rare and has been used only for the synthesis of condensed fluorinated pyrimidines.

In continuing our previous work in this field,[5b,g,h,8] we report here the use of 3-(polyfluoroacyl)chromones **1** as novel and versatile substrates for the assembly of a pyrimidine core bearing a polyfluoroalkyl substituent. These polyfluoroacylated compounds readily and reversibly form covalent hydrates **2**, as observed from their ^{1}H and ^{19}F NMR spectra, which contain two sets of signals.



Scheme 1 Routes to 3-(polyfluoroacyl)chromones and their hydrates

Chromones **1**, as mixtures with their corresponding hydrates **2**, are easily accessible compounds, and can be obtained either by trifluoroacetylation of (2*E*)-3-(dimethylamino)-1-(2-hydroxyphenyl)prop-2-en-1-one

(**3**; route A)[9] or by formylation of 2-hydroxy-2-(polyfluoroalkyl)chroman-4-ones **4** with diethoxymethyl acetate at 140–150 °C for 15 min (route B)[10] (Scheme 1). The structure of the hydrate **2** ($R^F = CF_3$) was confirmed unambiguously by means of a single crystal X-ray analysis (Figure 1).

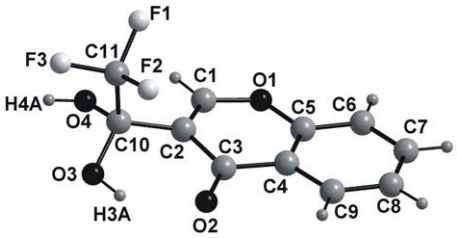
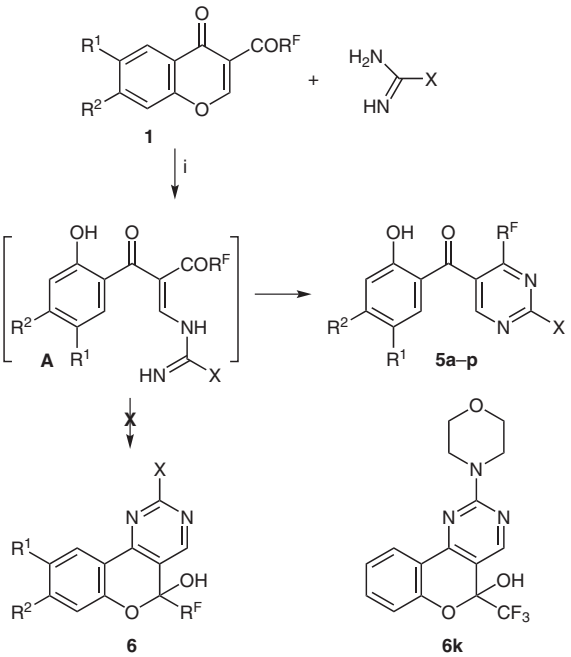


Figure 1 Molecular structure of hydrate **2** ($R^F = CF_3$)

To develop a new synthesis of polyfluoroalkyl-containing pyrimidines that could be used for the preparation of more-complex molecules, we studied the reaction of **1** with a number of 1,3-*NCN*-dinucleophiles. We found that treatment of chromones **1** with amidine or guanidine salts in the presence of sodium acetate in dry *N,N*-dimethylformamide at 80 °C for 12 h gave the corresponding 4-(polyfluoroalkyl)pyrimidines **5a**–**p** in 27–94% yields, after optimization. The first step of the reaction appears to involve an attack at the C-2 atom of the chromone by the amino function, with concomitant opening of the pyrone ring (1,4-addition; intermediate **A**). Subsequent intramolecular attack at the R^FCO group by the second nitrogen leads to 5-acylated 4-R^F-pyrimidines **5a**–**p** (Scheme 2, Table 1). Given the actual interest in fluoroheteroaromatics as pharmaceutical intermediates,[11] this novel entry to fluorinated pyrimidines is noteworthy and complements the published synthetic methods.



Scheme 2 *Reagents and conditions:* (i) DMF, 80 °C, 12 h.

Table 1 Synthesis of 4-(Polyfluoroalkyl)pyrimidines **5a–p** by Reaction of Chromones **1** with 1,3-*NCN*-Binucleophiles

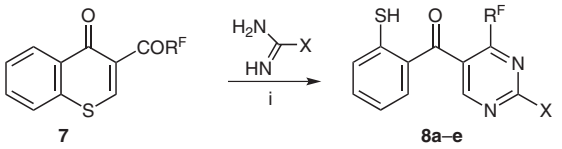
Pyrimidine	R^F	R^1	R^2	X	Yield (%)
5a	CF_3	H	H	H	87
5b	CF_3	H	H	Me	87
5c	CF_3	H	H	Ph	92
5d	CF_3	Me	H	Ph	49
5e	CF_3	Cl	H	Ph	44
5f	CF_3	H	MeO	Ph	58
5g	CF_3	H	H	4-HOC_6H_4	94
5h	CF_3	H	H	4-$H_2NC_6H_4$	92
5i	CF_3	H	H	NH_2	84
5j	CF_3	H	H	NMe_2	91
5k	CF_3	H	H	morpholino	80
5l	CF_2H	H	H	Ph	52
5m	$(CF_2)_2H$	H	H	Ph	68
5n	CF_2H	H	H	NH_2	57
5o	$(CF_2)_2H$	H	H	NH_2	27
5p	$(CF_2)_2CF_3$	H	H	Me	86

The alternative cyclization of **A** involving the imino group and the carbonyl carbon atom connected to the benzene ring to give 5*H*-chromeno[4,3-*d*]pyrimidin-5-ols **6** does not occur except in the case of morpholinoformamidine, where this pathway was observed and compound **6k** was isolated in 18% yield, in addition to product **5k**. Note that phenyl chromone-3-sulfonate undergoes a ring transformation with amidines to give the corresponding benzoxathiinopyrimidines.[12]

The structure and composition of 4-R^F-pyrimidines **5a**–**p** were confirmed by 1-dimensional (1D) ^1H, ^{19}F, and ^{13}C NMR spectroscopy, 2D NMR correlation spectroscopy (COSY), ^1H–^{13}C heteronuclear multiple bond correlation (HMBC) spectroscopy, atmospheric-pressure spray ionization (APSI) mass spectrometry, and elemental analysis. In the case of $R^F = CF_3$, the most convincing evidence for the formation of **5** was the chemical shift of C-4 (δ = 150–154 ppm) with a coupling constant $^2J_{C,F}$ = 35–37 Hz. In rotating-frame Overhauser effect spectroscopy (ROESY), a correlation of the pyrimidine proton in the 6-position (δ = 8.4–9.2 ppm) with the protons of the salicylic moiety was clearly observed. The ^{13}C NMR spectra of **5a**–**p** displayed a low-field signal at δ = 196–198 ppm in $CDCl_3$ and at δ = 192–194 ppm in DMSO-d_6 for the carbonyl group carbon. With regard to the structure of compound **6k**, the resonance of the sp^3-carbon atom was observed at 95.5 ppm with $^2J_{C,F}$ = 33 Hz.

The 3-(polyfluoroacyl)thiochromones **7**, which are thio analogues of **1**, are previously unknown compounds. We

recently elaborated a method for preparing these molecules from easily available thiochroman-4-one (2,3-dihydro-4*H*-1-benzothiopyran-4-one).[13] Thiochromones **7** are less reactive than **1**, but they are still able to react with amidines and guanidines salts under harsher conditions (*N,N*-dimethylformamide, 12 h, 100 °C) to give good yields of the corresponding pyrimidines **8a–e** (Scheme 3 and Table 2).

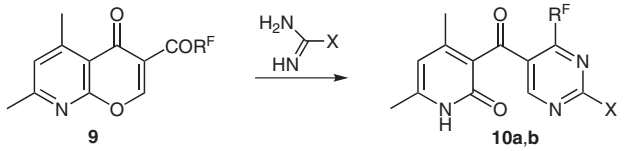


Scheme 3 *Reagents and conditions:* (i) DMF, 100 °C, 12 h.

Table 2 Synthesis of 4-(Polyfluoroalkyl)pyrimidines **8a–e** by Reaction of Thiochromones **7** with 1,3-*NCN*-Binucleophiles

Pyrimidine	R^F	X	Yield (%)
8a	CF_3	Ph	43
8b	CF_3	Me	57
8c	CF_3	NH_2	61
8d	CF_3	morpholino	58
8e	CF_2CF_3	Me	52

The proposed reaction was also found to be suitable for 8-aza-3-(polyfluoroacyl)chromones **9**,[14] which showed a similar reactivity with benzamidine or *O*-methylisourea as dinucleophiles. The reaction proceeds in refluxing ethanol in the presence of potassium hydroxide to give keto-linked bis-heterocycles **10a** and **10b**, which both contain a 2-pyridone ring and a pyrimidine ring (Scheme 4). Non-fluorinated analogues of **10** have previously been reported to be selective inhibitors of phosphodiesterase V.[15]



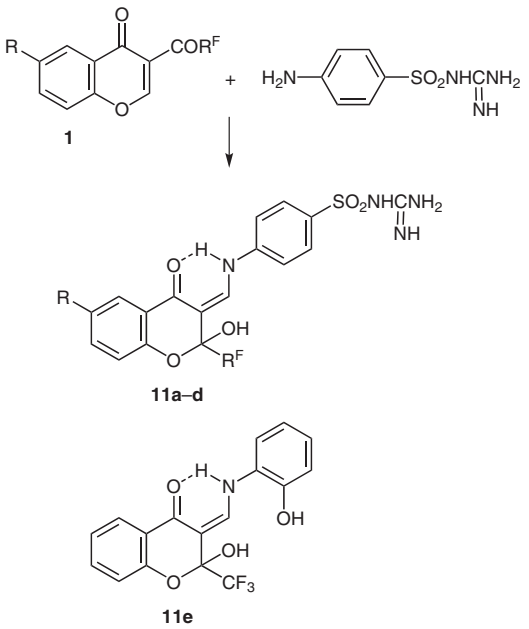
a: $R^F = CF_2H$, X = Ph (36%)
b: $R^F = CF_3$, X = OMe (38%)

Scheme 4 Synthesis of 3-{[4-(Fluoroalkyl)-pyrimidin-5-yl]carbonyl}-4,6-dimethylpyridin-2(1*H*)-ones

Reaction of chromones **1** with sulfaguanidine (4-amino-*N*-carbamimidoylbenzenesulfonamide; sulginum) in refluxing ethanol gave the chroman-4-one derivatives **11a–d**, and no formation of the corresponding pyrimidines was detected at all. Obviously, the presence of the sulfonyl group near the guanidino moiety strongly reduces the nucleophilicity of the latter, and the reaction proceeds with the participation of the amino group, as reported previously for aromatic amines[10] (Scheme 5, Table 3). Note that condensation of 3-formylchromones with sulfaguanidine[16] results in the formation of the corresponding Schiff's bases, the 3-[(4-guanidinosulfonyl)phenyliminomethyl]chromones. This different behavior is not unexpected, in that the presence of an R^F group will tend to complicate the dehydration stage.

The structures of adducts **11a–d** were determined by using spectral data for related compounds.[10] The IR spectra of **11a–d** showed absorption bands in the ranges 3450–3220 and 1646–1594 cm^{-1} arising from the OH and NH groups and the aminoenone fragment, respectively. A characteristic feature of the ^1H NMR spectra in DMSO-d_6 solution is the appearance of one singlet at δ = 8.5–9.2 ppm for the OH proton and two AX doublets (J_{AX} = 12.7 Hz) at δ = 7.9–8.0 and 12.5 ppm for the =CH and –NH protons, respectively. In the ^{19}F NMR spectrum, a singlet for the CF_3 group of **11b** appeared at –84.9 ppm, thereby confirming that this group is bonded to the sp^3-hybridized carbon atom.

In addition, to confirm the enamine structure of **11a–d**, an X-ray diffraction study was carried out on crystals of the product **11e** as a model compound prepared from 3-(trifluoroacetyl)chromone and 2-aminophenol (Figure 2).



Scheme 5 Synthesis of 2-Hydroxy-2-(polyfluoroalkyl)chroman-4-ones **11a–d**

Table 3 Synthesis of 2-Hydroxy-2-(polyfluoroalkyl)chroman-4-ones **11a–d** by Reaction of Chromones **1** with Sulfaguanidine

Chroman-4-one	R^F	R	Yield (%)
11a	CF_3	H	77
11b	CF_3	Me	86
11c	CF_2H	H	74
11d	$(CF_2)_2H$	H	72

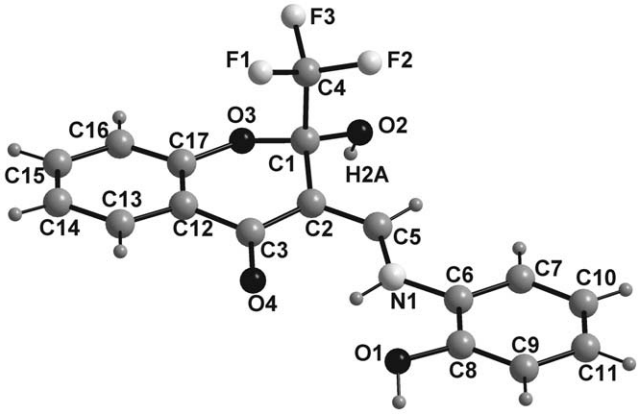
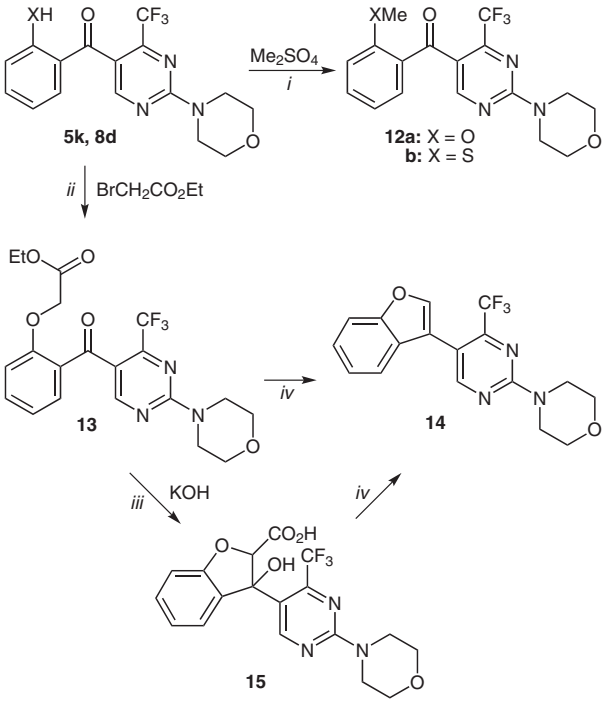


Figure 2 Molecular structure of compound **11e**

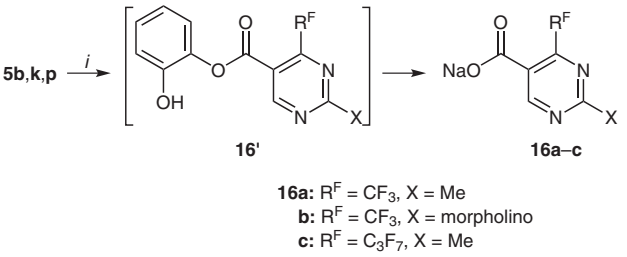
Next, in view of the fact that the pyrimidine ring is an important structural fragment of many natural and biologically active substances, we investigated some properties of compounds **5b**, **5k**, **5p**, and **8d** as representative examples. We found that 4-(trifluoromethyl)pyrimidines **5k** and **8d** reacted with an excess of dimethyl sulfate (3 equivalents) in refluxing toluene to afford the corresponding *O*- and *S*-methylated products **12a** and **12b** in high yields (70–77%). A remarkable feature in the ^{13}C NMR spectra of these compounds was the appearance of a quartet ($J_{C,F} = 2.6$ Hz for **12a** and $J_{C,F} = 2.2$ Hz for **12b**) assigned to the methyl group, showing that the methyl and trifluoromethyl groups are spatially close to one another, and confirming the structure of pyrimidines **12** (Scheme 6).

Derivatives of *ortho*-acylated phenols and thiophenols have recently been used in the synthesis of various benzofurans[17a] and benzothiophenes.[17b] We therefore investigated the synthesis of a benzofuran starting from pyrimidine **5k** (Scheme 6). First, **5k** was alkylated with ethyl bromoacetate in acetone containing potassium carbonate to give ether ester **13** as a colorless solid in a yield of 98%. When **13** was refluxed in glacial acetic acid, cyclization, hydrolysis, and decarboxylation took place to yield benzofuran **14**. However, when the reaction was conducted in dioxane with potassium hydroxide as a basic catalyst, followed by the addition of hydrochloric acid, the stable intermediate **15** could be isolated; this was easily converted into benzofuran derivative **14** by refluxing in glacial acetic acid.

Finally, it is worth mentioning that 4-(trifluoromethyl)pyrimidine-5-carboxylic acids and their derivatives are of interest because of their cardiotonic,[18a] antiviral, and antimycotic activities.[18b] Additionally, some members of this family have been recognized as a new class of potent ryanodine receptor activators[18c] and as inhibitors of AP-1 and NF-κB mediated gene expression.[18d,e] For this reason, the sodium salts of pyrimidine acids **16a–c** were prepared under Dakin reaction conditions as outlined in Scheme 7.[19]



Scheme 6 *Reagents and conditions:* (i) NaOH, K_2CO_3, Bu_4NHSO_4, Me_2SO_4, toluene, reflux, 20 h; (ii) K_2CO_3 (5 equiv), ethyl bromoacetate (1.5 equiv), acetone, r.t., 12 h; (iii) a) KOH, b) 2 M aq HCl; (iv) glacial HOAc, reflux, 24 h.



Scheme 7 *Reagents and conditions:* (i) THF, NaH (60% dispersion in mineral oil), H_2O_2 (35% aq).

Oxidation of a series of derivatives **5** by treatment with sodium hydride in tetrahydrofuran, followed by the addition of 35% aqueous hydrogen peroxide presumably led to the formation of the esters **16′**, which underwent hydrolysis during the acidic workup to afford the corresponding salts **16a–c**. The oxidation occurred slowly and was complete only after 96 h. The esters **16′** were detected by GC-MS as reaction intermediates; however, all our attempts to isolate these compounds failed. Sodium salts **16** were successfully isolated in high yields by column chromatography. Thus, compounds **5** are novel and convenient precursors for 4-R^F-pyrimidine-5-carboxylic acids.

In conclusion, the reactions of 3-R^FCO-chromones and their hetero analogues with amidines or guanidines were investigated systematically to provide a new simple and convenient synthetic route to 5-salicyloyl-4-(polyfluoroalkyl)pyrimidines. Oxidation of these compounds under Dakin reaction conditions yielded the corresponding 4-

R^F-pyrimidine-5-carboxylic acids as their sodium salts. The simple procedures and the high yields of the products allow the synthesis of functionalized fluorinated pyrimidines, which are interesting objects for medicine chemistry and drug discovery.

IR spectra were recorded on a Perkin-Elmer Spectrum BX-II instrument as KBr disks. ^{1}H (400 MHz), ^{13}C (100 MHz), and ^{19}F (376 MHz) NMR spectra were recorded on a Bruker DRX-400 spectrometer in $CDCl_3$ or DMSO-d_6 solutions with TMS and $CFCl_3$ as internal standards, respectively. Mass spectra were obtained on a Hewlett-Packard HPGC/MS 5890/5972 instrument (EI, 70 eV) by GC inlet or on a MX-1321 instrument (EI, 70 eV) by direct inlet. 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 the solvents that were used were dried and distilled according to standard procedures. Column chromatography was performed on silica gel (63–200 mesh, Merck). Silica gel Merck 60F254 plates were used for TLC. Satisfactory microanalyses were obtained: C ± 0.33; H ± 0.45; N ± 0.25.

Crystal Data for 2 and 11e

Crystallographic measurements were performed at room temperature on an Enraf-Nonius CAD4 diffractometer operating in the ω-2θ scan mode (the scanning rate ratio ω/2θ = 1.2). The structure was solved by direct methods, and refined by the full-matrix least-squares technique in an anisotropic approximation using SHELXS97 and SHELXL9722 program packages. Hydrogen atoms were placed at calculated positions and refined by means of a 'riding' model.

Crystal data for **2**: triclinic, $P\bar{1}$, a = 7.7360(15), b = 7.9747(16), c = 8.4549(17) Å, α = 106.02(3)°, β = 91.66(3)°, γ = 103.63(3)°, V = 484.74(17) Å^3, Z = 2, μ(Mo-Kα) = 0.171 mm^{-1}. 7071 reflections collected, 2046 unique reflections, [R_{int} = 0.0448), Mo-Kα radiation (λ = 0.71073 Å), 163 parameters, $R1$ = 0.0341, $wR2$ = 0.0879, S = 1.076 (1921 reflections with $I > 2\sigma(I)$].

Crystal data of **11e**: triclinic, $P\bar{1}$, a = 6.2331(12), b = 8.8727(18), c = 13.966(3) Å, α = 100.15(3)°, β = 96.47(3)°, γ = 104.92(3)°, V = 724.4(2) Å^3, Z = 2, μ(Mo-Kα) = 0.140 mm^{-1}. 9551 reflections collected, 2726 unique reflections, [R_{int} = 0.0798), Mo-Kα radiation (λ = 0.71073 Å), 226 parameters, $R1$ = 0.0554, $wR2$ = 0.1097, S = 1.074 (1981 reflections with $I > 2\sigma(I)$].

Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Center as Supplementary Publication No. CCDC 720749 for **2** and CCDC 720808 for **11e**, and can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(1223)336033; e-mail: deposit@ccdc.cam.ac.uk].

Compounds 5a–p and 8a–e; General Procedure

A mixture of **1** or **7** (1 mmol), the dinucleophile in the form of a salt (1 mmol), and NaOAc (1 mmol) in dry DMF (7 mL) was stirred at 80–100 °C overnight. The progress of the reaction was monitoring by TLC. The solvent was removed in vacuo, and the residue was purified by flash chromatography (silica gel) or recrystallization (heptane–toluene).

5-Salicyloyl-4-(trifluoromethyl)pyrimidine (5a)

Yield: 233 mg (87%); colorless solid; mp 109–111 °C; R_f = 0.37 (Et_2O).

^{1}H NMR ($CDCl_3$): δ = 6.88 (ddd, ^3J = 8.0, 7.4 Hz, ^4J = 0.9 Hz, 1 H, H-5′), 7.05 (dd, ^3J = 8.0 Hz, ^4J = 1.6 Hz, 1 H, H-6′), 7.10 (dd, ^3J = 8.4 Hz, ^4J = 0.9 Hz, 1 H, H-3′), 7.58 (ddd, ^3J = 8.4, 7.4 Hz, ^4J = 1.7 Hz, 1 H, H-4′), 8.93 (s, 1 H, H-6), 9.51 (s, 1 H, H-2), 11.50 (s, 1 H, OH).

^{13}C NMR ($CDCl_3$): δ = 119.0, 119.2 (q, $^5J_{C,F}$ = 0.8 Hz), 119.7, 120.1 (q, $^1J_{C,F}$ = 277.0 Hz), 129.6 (q, $^3J_{C,F}$ = 1.2 Hz), 132.6, 138.5, 152.1 (q, $^2J_{C,F}$ = 37.0 Hz), 157.4, 159.6, 163.4, 195.9.

MS (EI, 70 eV): *m/z* (%) = 268 (68) [M]$^+$, 199 (77) [M – CF_3]$^+$, 172 (16), 121 (100) [HOC_6H_4CO]$^+$, 93 (18) [C_6H_4CO]$^+$, 65 (23).

2-Methyl-5-salicyloyl-4-(trifluoromethyl)pyrimidine (5b)

Yield: 246 mg (87%); colorless solid; mp 87–89 °C; R_f = 0.29 (PE–EtOAc, 2:1).

^{1}H NMR ($CDCl_3$): δ = 2.91 (s, 3 H, Me), 6.86 (t, ^3J = 7.8 Hz, 1 H, H-5′), 7.08 (d, ^3J = 7.8 Hz, 2 H, H-3′, H-6′), 7.56 (t, ^3J = 7.8 Hz, 1 H, H-4′), 8.80 (s, 1 H, H-6), 11.57 (s, 1 H, OH).

^{13}C NMR ($CDCl_3$): δ = 26.0, 118.9, 119.4 (q, $^5J_{C,F}$ = 0.8 Hz), 119.6, 120.0 (q, $^1J_{C,F}$ = 277.0 Hz), 126.5 (q, $^3J_{C,F}$ = 1.2 Hz), 132.6, 138.2, 152.1 (q, $^2J_{C,F}$ = 36.0 Hz), 157.3, 163.2, 170.2, 196.6.

^{19}F NMR ($CDCl_3$): δ = –66.0 (s, CF_3).

MS (EI, 70 eV): *m/z* (%) = 282 (32) [M]$^+$, 214 (15) [M + 1 – CF_3]$^+$, 213 (100) [M – CF_3]$^+$, 172 (21), 121 (81) [HOC_6H_4CO]$^+$, 93 (13) [HOC_6H_4]$^+$, 65 (17).

2-Phenyl-5-salicyloyl-4-(trifluoromethyl)pyrimidine (5c)

Yield: 317 mg (92%); colorless solid; mp 100–102 °C; R_f = 0.65 (Et_2O).

^{1}H NMR ($CDCl_3$): δ = 6.88 (t, ^3J = 7.8 Hz, 1 H, H-5′), 7.11 (d, ^3J = 7.8 Hz, 1 H, H-6′), 7.19 (d, ^3J = 7.8 Hz, 1 H, H-3′), 7.52–7.60 (m, 4 H, H-4′, Ph), 8.55 (m, 2 H, Ph), 8.93 (s, 1 H, H-6), 11.63 (s, 1 H, OH).

^{13}C NMR ($CDCl_3$): δ = 118.9, 119.5 (q, $^5J_{C,F}$ = 0.8 Hz), 119.6, 120.3 (q, $^1J_{C,F}$ = 277.0 Hz), 126.7 (q, $^3J_{C,F}$ = 1.2 Hz), 129.0, 129.0, 132.6, 132.7, 135.3, 138.3, 152.7 (q, $^2J_{C,F}$ = 36.0 Hz), 157.9, 163.3, 165.9, 196.9.

^{19}F NMR ($CDCl_3$): δ = –66.1 (s, CF_3).

MS (EI, 70 eV): *m/z* (%) = 344 (29) [M]$^+$, 276(19) [M + 1 – CF_3]$^+$, 275 (100) [M – CF_3]$^+$, 121 (47) [HOC_6H_4CO]$^+$, 120 (28) [OC_6H_4CO]$^+$, 93 (10) [HOC_6H_4]$^+$, 65 (11).

5-(2-Hydroxy-5-methylbenzoyl)-2-phenyl-4-(trifluoromethyl)pyrimidine (5d)

Yield: 176 mg (49%); colorless crystals; mp 133–134 °C.

IR (KBr): 1635, 1574, 1533, 1484 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 2.22 (s, 3 H, Me), 6.94 (br d, 1 H, H-6′), 7.02 (d, ^3J = 8.6 Hz, 1 H, H-3′), 7.40 (dd, ^3J = 8.6, ^4J = 2.1 Hz, 1 H, H-4′), 7.53–7.62 (m, 3 H, Ph), 8.57–8.61 (m, 2 H, Ph), 8.94 (s, 1 H, H-6), 11.49 (s, 1 H, OH).

^{13}C NMR (DMSO-d_6): δ = 19.7, 117.6, 120.5 (q, $^1J_{C,F}$ = 276.2 Hz), 121.5, 128.2, 128.5, 129.1, 130.8, 131.0, 132.2, 135.2, 138.0, 150.1 (q, $^2J_{C,F}$ = 35.3 Hz), 157.8, 158.4, 163.5, 191.9.

5-(5-Chloro-2-hydroxybenzoyl)-2-phenyl-4-(trifluoromethyl)pyrimidine (5e)

Yield: 167 mg (44%); yellow crystals; mp 117–118 °C.

IR (KBr): 1634, 1570, 1540, 1463 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.09 (d, ^3J = 9.0 Hz, 1 H, H-3′), 7.16 (d, ^4J = 2.5 Hz, 1 H, H-6′), 7.54 (dd, ^3J = 9.0 Hz, ^4J = 2.5 Hz, 1 H, H-4′), 7.54–7.63 (m, 3 H, Ph), 8.57–8.61 (m, 2 H, Ph), 8.95 (s, 1 H, H-6), 11.57 (s, 1 H, OH).

5-(2-Hydroxy-4-methoxybenzoyl)-2-phenyl-4-(trifluoromethyl)pyrimidine (5f)
Yield: 155 mg (58%); colorless crystals; mp 108–109 °C.

IR (KBr): 1620, 1606, 1572, 1533, 1512, 1500 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 3.88 (s, 3 H, MeO), 6.42 (dd, ^3J = 9.0 Hz, ^4J = 2.4 Hz, 1 H, H-5′), 6.54 (d, ^4J = 2.4 Hz, 1 H, H-3′), 7.08 (d, ^3J = 9.0 Hz, 1 H, H-6′), 7.52–7.61 (m, 3 H, Ph), 8.55–8.58 (m, 2 H, Ph), 8.93 (s, 1 H, H-6), 12.14 (s, 1 H, OH).

^{19}F NMR ($CDCl_3$): δ = –66.9 (s, CF_3).

2-(4-Hydroxyphenyl)-5-salicyloyl-4-(trifluoromethyl)pyrimidine (5g)
Yield: 339 mg (94%); colorless solid; mp 182–184 °C; R_f = 0.59 (Et_2O).

^1H NMR (DMSO-d_6): δ = 6.94–7.00 (m, 4 H, H-3′, H-5′, Ar), 7.56 (t, ^3J = 7.8 Hz, 1 H, H-4′), 7.73 (d, ^3J = 7.8 Hz, 1 H, H-6′), 8.30 (d, ^3J = 8.1 Hz, 2 H, Ar), 9.11 (s, 1 H, H-6), 10.31 (s, 1 H, OH), 10.78 (s, 1 H, OH).

^{13}C NMR (DMSO-d_6): δ = 115.8, 117.5, 119.5, 120.4 (q, $^1J_{C,F}$ = 275.0 Hz), 122.0, 126.1, 129.1, 130.2, 131.4, 136.7, 150.1 (q, $^2J_{C,F}$ = 35.0 Hz), 158.2, 159.6, 161.4, 163.8, 192.4.

^{19}F NMR (DMSO-d_6): δ = –65.6 (s, CF_3).

MS (EI, 70 eV): *m/z* (%) = 361 (20) $[M + 1]^+$, 360 (90) $[M]^+$, 292 (24) $[M + 1 – CF_3]^+$, 291 (95) $[M – CF_3]^+$, 240 (34), 121 (100) $[HOC_6H_4CO]^+$, 120 (36) $[OC_6H_4CO]^+$, 93 (23) $[HOC_6H_4]^+$, 65 (22).

2-(4-Aminophenyl)-5-salicyloyl-4-(trifluoromethyl)pyrimidine (5h)
Yield: 331 mg (92%); colorless solid; mp 160–162 °C; R_f = 0.52 (Et_2O).

^1H NMR (DMSO-d_6): δ = 6.94–7.00 (m, 4 H, H-3′, H-5′, Ar), 7.56 (t, ^3J = 7.8 Hz, 1 H, H-4′), 7.62 (br s, 2 H, NH_2), 7.73 (d, ^3J = 7.8 Hz, 1 H, H-6′), 8.14 (d, ^3J = 8.1 Hz, 2 H, Ar), 8.98 (s, 1 H, H-6), 10.78 (s, 1 H, OH).

^{13}C NMR (DMSO-d_6): δ = 113.4, 117.5, 119.4, 120.4 (q, $^1J_{C,F}$ = 276.0 Hz), 122.0, 122.1, 127.6 (q, $^3J_{C,F}$ = 1.0 Hz), 130.1, 131.5, 136.5, 150.1 (q, $^2J_{C,F}$ = 35.0 Hz), 153.0, 158.1, 159.6, 163.3, 192.9.

^{19}F NMR (DMSO-d_6): δ = –65.6 (s, CF_3).

MS (EI, 70 eV): *m/z* (%) = 360 (30) $[M + 1]^+$, 359 (89) $[M]^+$, 290 (16), 290 (70) $[M – CF_3]^+$, 240 (15), 239 (100), 121 (40) $[HOC_6H_4CO]^+$, 118 (28), 93 (12) $[HOC_6H_4]^+$, 65 (13).

2-Amino-5-salicyloyl-4-(trifluoromethyl)pyrimidine (5i)
Yield: 238 mg, (84%); colorless solid; mp 206–208 °C; R_f = 0.58 (Et_2O).

^1H NMR (DMSO-d_6): δ = 6.95 (t, ^3J = 7.8 Hz, 1 H, H-5′), 6.97 (d, ^3J = 8.2 Hz, 1 H, H-3′), 7.50–7.56 (m, 2 H, H-4′, H-6′), 7.85 (br s, 2 H, NH_2), 8.47 (s, 1 H, H-6), 10.82 (s, 1 H, OH).

^{13}C NMR (DMSO-d_6): δ = 117.4, 119.2, 119.7 (q, $^3J_{C,F}$ = 1.2 Hz), 120.2 (q, $^1J_{C,F}$ = 276.0 Hz), 122.3, 131.8, 135.9, 152.3 (q, $^2J_{C,F}$ = 35.0 Hz), 159.5, 160.5, 163.1, 194.2.

^{19}F NMR (DMSO-d_6): δ = –65.6 (s, CF_3).

MS (EI, 70 eV): *m/z* (%) = 283 (35) $[M]^+$, 215 (13) $[M + 1 – CF_3]^+$, 214 (85) $[M – CF_3]^+$, 190 (35) $[M – HOC_6H_4]^+$, 163 (13) $[M + 1 – HOC_6H_4CO]^+$, 121 (70) $[HOC_6H_4CO]^+$, 120 (100) $[OC_6H_4CO]^+$, 93 (25) $[HOC_6H_4]^+$, 92 (41), 65 (33).

2-(Dimethylamino)-5-salicyloyl-4-(trifluoromethyl)pyrimidine (5j)
Yield: 283 mg (91%); colorless solid; mp 119–120 °C; R_f = 0.23 (PE–Et_2O, 1:1).

^1H NMR ($CDCl_3$): δ = 3.26 (s, 6 H, 2 Me), 6.83 (t, ^3J = 7.8 Hz, 1 H, H-5′), 7.01 (d, ^3J = 7.8 Hz, 1 H, H-3′), 7.32 (d, ^3J = 7.8 Hz, 1 H, H-6′), 7.48 (t, ^3J = 7.8 Hz, 1 H, H-4′), 8.41 (s, 1 H, H-6), 11.84 (s, 1 H, OH).

^{13}C NMR ($CDCl_3$): δ = 37.0, 116.6 (q, $^3J_{C,F}$ = 1.0 Hz), 118.5, 119.1, 119.9, 120.2 (q, $^1J_{C,F}$ = 276.0 Hz), 132.7, 137.4, 154.1 (q, $^2J_{C,F}$ = 36.0 Hz), 159.5, 161.4 (q, $^4J_{C,F}$ = 0.8 Hz), 163.1, 198.0.

MS (EI, 70 eV): *m/z* (%) = 311 (21) $[M]^+$, 242 (89) $[M – CF_3]^+$, 191 (100) $[M + 1 – HOC_6H_4CO]^+$, 190 (34) $[M – HOC_6H_4CO]^+$, 121 (51) $[HOC_6H_4CO]^+$, 120 (13) $[OC_6H_4CO]^+$, 93 (11) $[HOC_6H_4]^+$.

2-Morpholin-4-yl-5-salicyloyl-4-(trifluoromethyl)pyrimidine (5k)
Yield: 263 mg (80%); colorless solid; mp 137–139 °C; R_f = 0.31 (PE–Et_2O, 1:1).

^1H NMR ($CDCl_3$): δ = 3.79 (dd, ^3J = 5.1, 4.6 Hz, 4 H, morpholino), 3.94 (dd, ^3J = 5.1, 4.6 Hz, 4 H, morpholino), 6.86 (td, ^3J = 7.8 Hz, ^4J = 0.8 Hz, 1 H, H-5′), 7.05 (dd, ^3J = 8.2 Hz, ^4J = 0.8 Hz, 1 H, H-3′), 7.31 (dd, ^3J = 7.8 Hz, ^4J = 1.6 Hz, 1 H, H-6′), 7.53 (td, ^3J = 7.8 Hz, ^4J = 1.6 Hz, 1 H, H-4′), 8.43 (s, 1 H, H-6), 11.80 (s, 1 H, OH).

^{13}C NMR ($CDCl_3$): δ = 44.2, 69.6, 117.7 (q, $^3J_{C,F}$ = 1.0 Hz), 118.7, 118.8, 119.2, 119.8 (q, $^5J_{C,F}$ = 0.6 Hz), 120.2 (q, $^1J_{C,F}$ = 277.0 Hz), 132.8, 137.5, 154.3 (q, $^2J_{C,F}$ = 36.0 Hz), 159.7, 160.8 (q, $^4J_{C,F}$ = 1.0 Hz), 163.2, 197.6.

MS (EI, 70 eV): *m/z* (%) = 353 (48) $[M]^+$, 322 (15), 284 (61) $[M – CF_3]^+$, 233 (42) $[M + 1 – HOC_6H_4CO]^+$, 232 (48) $[M – HOC_6H_4CO]^+$, 226 (28), 203 (15), 202 (39), 176 (19), 121 (100) $[HOC_6H_4CO]^+$, 120 (60) $[OC_6H_4CO]^+$, 93 (25) $[HOC_6H_4]^+$, 92 (20), 57 (19), 56 (25), 43 (19).

2-Morpholin-4-yl-5-(trifluoromethyl)-5*H*-chromeno[4,3-*d*]pyrimidin-5-ol (6k)
This substance was obtained as a byproduct in the synthesis of **5k**.

Yield: 61 mg (18%); colorless solid; mp 143–147 °C; R_f = 0.23 (PE–Et_2O, 1:1).

^1H NMR ($CDCl_3$): δ = 3.7–3.9 (br m, 8 H, morpholino), 5.19 (s, 1 H, OH), 7.04 (dd, ^3J = 8.0 Hz, ^4J = 0.9 Hz, 1 H, H-7), 7.11 (td, ^3J = 7.8 Hz, ^4J = 0.9 Hz, 1 H, H-9), 7.43 (dt, ^3J = 7.8 Hz, ^4J = 1.7 Hz, 1 H, H-8), 8.13 (dd, ^3J = 7.8 Hz, ^4J = 1.7 Hz, 1 H, H-10), 8.42 (s, 1 H, H-4).

^{13}C NMR (DMSO-d_6): δ = 44.1 (2C), 66.6 (2C), 95.5 (q, $^2J_{C,F}$ = 33.0 Hz), 107.8, 117.7, 120.2, 122.4 (q, $^1J_{C,F}$ = 287.0 Hz), 122.8, 124.9, 133.8, 153.8, 155.4, 156.9, 157.0.

MS (EI, 70 eV): *m/z* (%) = 353 (48) $[M]^+$, 322 (15), 284 (61) $[M – CF_3]^+$, 233 (42) $[M + 1 – HOC_6H_4CO]^+$, 232 (48) $[M – HOC_6H_4CO]^+$, 226 (28), 203 (15), 202 (39), 176 (19), 121 (100) $[HOC_6H_4CO]^+$, 120 (60) $[OC_6H_4CO]^+$, 93 (25) $[HOC_6H_4]^+$, 92 (20), 57 (19), 56 (25), 43 (19).

4-(Difluoromethyl)-2-phenyl-5-salicyloylpyrimidine (5l)
Yield: 160 mg (52%); colorless crystals; mp 105–106 °C.

IR (KBr): 1618, 1570, 1541, 1483 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 6.98–7.06 (m, 2 H, H-3′, H-5′), 7.19 (t, $^2J_{H,F}$ = 53.4 Hz, 1 H, CF_2H), 7.58 (ddd, ^3J = 8.3, 7.3 Hz, ^4J = 1.7 Hz, 1 H, H-4′), 7.59–7.65 (m, 3 H, Ph), 7.68 (dd, ^3J = 8.2 Hz, ^4J = 1.7 Hz, 1 H, H-6′), 8.47–8.50 (m, 2 H, Ph), 9.12 (s, 1 H, H-6), 10.80 (s, 1 H, OH).

^{19}F NMR (DMSO-d_6): δ = –118.9 (d, $^2J_{F,H}$ = 53.4 Hz, CF_2H).

2-Phenyl-4-(1,1,2,2-tetrafluoroethyl)-5-salicyloylpyrimidine (5m)
Yield: 256 mg (68%); yellow needles; mp 135–136 °C.

IR (KBr): 1625, 1605, 1569, 1529, 1489 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 6.95–7.02 (m, 2 H, H-3′, H-5′), 7.28 (tt, $^2J_{H,F}$ = 51.6 Hz, $^3J_{H,F}$ = 6.0 Hz, 1 H, CF_2CF_2H), 7.58 (ddd, ^3J = 8.4, 7.3 Hz, ^4J = 1.7 Hz, 1 H, H-4′), 7.60–7.68 (m, 3 H, Ph), 7.75 (dd, ^3J = 7.9 Hz, ^4J = 1.7 Hz, 1 H, H-6′), 8.51–8.54 (m, 2 H, Ph), 9.23 (s, 1 H, H-6), 10.80 (s, 1 H, OH).

2-Amino-4-(difluoromethyl)-5-salicyloylpyrimidine (5n)
Yield: 160 mg (57%); colorless shining crystals; mp 235–236 °C.

IR (KBr): 3337, 3198, 1673, 1622, 1586, 1541, 1519, 1484 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 6.93–6.99 (m, 2 H, H-3′, H-5′), 7.13 (t, $^2J_{H,F}$ = 53.7 Hz, 1 H, CF_2H), 7.43 (dd, ^3J = 7.7 Hz, ^4J = 1.6 Hz, 1 H, H-6′), 7.47 (ddd, ^3J = 8.4, 7.4 Hz, ^4J = 1.7 Hz, 1 H, H-4′), 7.88 (br s, 2 H, NH_2), 8.37 (s, 1 H, H-6), 10.51 (s, 1 H, OH).

^{13}C NMR (DMSO-d_6): δ = 110.1 (t, $^1J_{C,F}$ = 239.9 Hz), 117.0, 119.0 (t, $^3J_{C,F}$ = 3.3 Hz), 119.4, 124.1, 131.1, 134.3, 157.3, 159.9 (t, $^2J_{C,F}$ = 22.1 Hz), 162.7, 163.5, 193.4.

2-Amino-4-(1,1,2,2-tetrafluoroethyl)-5-salicyloylpyrimidine (5o)
Yield: 110 mg (27%); colorless crystals; mp 168–169 °C.

IR (KBr): 3370, 3333, 3193, 3162, 1666, 1631, 1607, 1582, 1537, 1516, 1488 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 6.85 (tt, $^2J_{H,F}$ = 52.4 Hz, $^3J_{H,F}$ = 6.0 Hz, 1 H, CF_2CF_2H), 6.93–7.00 (m, 2 H, H-3′, H-5′), 7.51 (dd, ^3J = 7.9 Hz, ^4J = 1.7 Hz, 1 H, H-6′), 7.54 (ddd, ^3J = 8.4, 7.3 Hz, ^4J = 1.7 Hz, 1 H, H-4′), 7.75 (br s, 2 H, NH_2), 8.46 (s, 1 H, H-6), 10.93 (s, 1 H, OH).

2-Methyl-5-salicyloyl-4-(perfluoropropyl)pyrimidine (5p)
Yield: 329 mg (86%); colorless solid; mp 81–84 °C; R_f = 0.27 (PE–Et_2O, 2:1).

^1H NMR ($CDCl_3$): δ = 2.90 (s, 3 H, Me), 6.84 (td, ^3J = 7.8 Hz, ^4J = 0.8 Hz, 1 H, H-5′), 7.03 (dd, ^3J = 7.8 Hz, ^4J = 1.4 Hz, 1 H, H-6′), 7.07 (dd, ^3J = 8.0 Hz, ^4J = 0.8 Hz, 1 H, H-3′), 7.55 (td, ^3J = 7.8 Hz, ^4J = 1.4 Hz, 1 H, H-4′), 8.77 (s, 1 H, H-6), 11.56 (s, 1 H, OH).

^{13}C NMR ($CDCl_3$): δ = 25.8, 108.7 (tqt, $^1J_{C,F}$ = 269.0 Hz, $^2J_{C,F}$ = 38.0, 36.0 Hz), 112.6 (tt, $^1J_{C,F}$ = 260.0 Hz, $^2J_{C,F}$ = 32.0 Hz), 117.6 (ttq, $^1J_{C,F}$ = 288.0 Hz, $^2J_{C,F}$ = 34.0 Hz, $^3J_{C,F}$ = 1.2 Hz), 118.9, 119.5, 119.7 (t, $J_{C,F}$ = 1.1 Hz), 128.2 (t, $^5J_{C,F}$ = 1.2 Hz), 132.7, 138.1, 152.4 (t, $^2J_{C,F}$ = 27.0 Hz), 157.4, 163.2, 169.8, 196.8.

MS (EI, 70 eV): *m/z* (%) = 382 (25) $[M]^+$, 381 (72) $[M–1]^+$, 214 (17) $[M + 1 – C_3F_7]^+$, 213 (100) $[M – C_3F_7]^+$.

5-(2-Sulfanylbenzoyl)-2-phenyl-4-(trifluoromethyl)pyrimidine (8a)
Yield: 155 mg (43%); colorless crystals; mp 192–193 °C.

IR (KBr): 3068, 1589, 1578, 1566, 1533 cm^{-1}.

^1H NMR (DMSO-d_6) δ = 7.46–7.58 (m, H-3′, H-4′, H-5′, 3 H), 7.58–7.64 (m, 3 H, Ph), 8.56–8.60 (m, 2 H, Ph), 8.73 (d, ^3J = 7.5 Hz, 1 H, H-6′), 9.20 (s, 1 H, H-6), 9.28 (br s, 1 H, SH).

MS (EI, 70 eV): *m/z* (%) = 360 $[M]^+$ (18), 292 $[M + 1 – CF_3]^+$ (10), 291 $[M – CF_3]^+$ (100), 224 (55), 223 (70), 137 $[HSC_6H_4CO]^+$ (15), 136 $[SC_6H_4CO]^+$ (28), 109 $[HSC_6H_4]^+$ (10), 65 (11).

5-(2-Sulfanylbenzoyl)-2-methyl-4-(trifluoromethyl)pyrimidine (8b)
Yield: 170 mg (57%); colorless solid; mp 179–181 °C; R_f = 0.78 (PE–Et_2O, 1:1).

^1H NMR (DMSO-d_6): δ = 2.30 (s, 3 H, Me), 7.49–7.66 (m, 3 H, H-3′, H-4′, H-5′), 8.57 (d, ^3J = 7.5 Hz, 1 H, H-6′), 9.00 (s, 1 H, H-6), 9.28 (br s, 1 H, SH).

^{13}C NMR (DMSO-d_6): δ = 25.9, 115.0 (q, $^3J_{C,F}$ = 1.4 Hz), 120.3 (q, $^1J_{C,F}$ = 277.0 Hz), 122.1, 122.3, 128.3, 135.0, 139.1, 154.3 (q, $^2J_{C,F}$ = 36.0 Hz), 162.7, 160.7, 165.3, 189.4.

MS (EI, 70 eV): *m/z* (%) 298 (33) $[M]^+$, 230 (17) $[M + 1 – CF_3]^+$, 229 (88) $[M – CF_3]^+$, 190 (100), 189 (71), 162 (55), 137 (31) $[HSC_6H_4CO]^+$, 136 (13) $[SC_6H_4CO]^+$, 109 (10) $[HSC_6H_4]^+$, 65 (14).

2-Amino-5-(2-sulfanylbenzoyl)-4-(trifluoromethyl)pyrimidine (8c)
Yield: 183 mg (61%); colorless solid; mp 219–221 °C; R_f = 0.65 (Et_2O).

^1H NMR (DMSO-d_6) δ = 7.39–7.56 (m, 3 H, H-3′, H-4′, H-5′), 7.93 (br s, 2 H, NH_2), 8.50 (d, ^3J = 7.5 Hz, 1 H, H-6′), 9.10 (s, 1 H, H-6), 9.42 (br s, 1 H, SH).

^{13}C NMR ($CDCl_3$): δ = 112.0 (q, $^3J_{C,F}$ = 1.2 Hz), 120.9 (q, $^1J_{C,F}$ = 277.0 Hz), 121.8, 122.5, 132.0, 136.1, 137.9, 153.7 (q, $^2J_{C,F}$ = 36.0 Hz), 160.9, 162.6, 164.2, 190.5.

MS (EI, 70 eV): *m/z* (%) 299 (100) $[M]^+$, 231 (20) $[M + 1 – CF_3]^+$, 230 (49) $[M – CF_3]^+$, 191 (14), 163 (15), 137 (30) $[HSC_6H_4CO]^+$, 136 (45) $[SC_6H_4CO]^+$, 109 (10) $[HSC_6H_4]^+$.

2-(Morpholin-4-yl)-5-(2-sulfanylbenzoyl)-4-(trifluoromethyl)pyrimidine (8d)
Yield: 214 mg (58%); colorless solid; mp 147–150 °C; R_f = 0.47 (PE–Et_2O, 1:1).

^1H NMR (DMSO-d_6) δ = 3.72 (dd, ^3J = 5.0, 4.8 Hz, 4 H, morpholino), 3.99 (dd, ^3J = 5.0, 4.8 Hz, 4 H, morpholino), 7.41–7.56 (m, 3 H, H-3′, H-4′, H-5′), 8.34 (d, ^3J = 7.8 Hz, 1 H, H-6′), 8.88 (s, 1 H, H-6), 9.27 (br s, 1 H, SH).

^{13}C NMR ($CDCl_3$): δ = 41.3, 68.9, 112.7 (q, $^3J_{C,F}$ = 1.6 Hz), 120.2 (q, $^1J_{C,F}$ = 277.0 Hz), 122.1, 122.7, 129.1, 135.4, 137.4, 154.1 (q, $^2J_{C,F}$ = 36.0 Hz), 159.3, 162.2, 162.1, 190.1.

MS (EI, 70 eV): *m/z* (%) 369 (100) $[M]^+$, 301 (55) $[M + 1 – CF_3]^+$, 300 (100) $[M – CF_3]^+$, 261 (31), 233 (15), 137 $[HSC_6H_4CO]^+$ (30), 136 $[SC_6H_4CO]^+$ (45), 109 $[HSC_6H_4]^+$ (10).

5-(2-Sulfanylphenyl)-2-methyl-4-(pentafluoroethyl)pyrimidine (8e)
Yield: 177 mg (52%); pink crystals; mp 123–127 °C; R_f = 0.40 (Et_2O).

^1H NMR ($CDCl_3$): δ = 2.15 (s, 3 H, Me), 7.29 (t, ^3J = 7.6 Hz, 1 H, H-5′), 7.35 (t, ^3J = 7.8 Hz, 1 H, H-4′), 7.93 (d, ^3J = 8.2 Hz, 1 H, H-3′), 8.38 (d, ^3J = 7.8 Hz, 1 H, H-6′), 8.66 (s, 1 H, H-6).

^{13}C NMR ($CDCl_3$): δ = 30.7, 108.3 (tq, $^1J_{CF}$ = 254 Hz, $^2J_{CF}$ = 38 Hz), 114.2, 117.6 (qt, $^1J_{CF}$ = 283 Hz, $^2J_{CF}$ = 36 Hz), 125.5, 126.4, 127.2, 127.9, 133.9, 141.8, 156.8 (t, $^2J_{CF}$ = 28 Hz), 160.5, 162.6, 192.3.

MS (EI, 70 eV): *m/z* (%) = 348 (21) $[M]^+$, 230 (33) $[M – C_2F_5 + 1]^+$, 229 (100) $[M – C_2F_5]^+$, 200 (22).

3-{[4-(Difluoromethyl)-2-phenylpyrimidin-5-yl]carbonyl}-4,6-dimethylpyridin-2(1*H*)-one (10a)
A soln of azachromone **9** (R^F = CF_2H; 100 mg, 0.4 mmol) in EtOH (7 mL) was added to a soln of benzamidine hydrochloride (150 mg, 0.79 mmol) and KOH (70 mg, 1.25 mmol) in EtOH (5 mL). The mixture was refluxed for 3 h, concentrated to dryness, and purified by chromatography on a short silica gel column using toluene as the mobile phase. On cooling the soln, yellow crystals that formed were filtered off and dried; yield: 50 mg (36%); mp 227–228 °C.

^1H NMR (DMSO-d_6): δ = 2.24 (d, J = 0.5 Hz, 3 H, Me), 2.32 (s, 3 H, Me), 6.19 (s, 1 H, H-5′), 7.19 (t, $^2J_{H,F}$ = 53.3 Hz, 1 H, CF_2H), 7.57–7.63 (m, 3 H Ph), 8.44–8.47 (m, 2 H, Ph), 9.03 (s, 1 H, H-6), 12.02 (s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 18.7, 20.4, 109.3, 110.8 (t, $^{1}J_{C,F}$ = 240.6 Hz, CF_2H), 121.7, 128.2, 129.0, 130.5 (t, $^{3}J_{C,F}$ = 2.9 Hz), 132.0, 135.8, 150.7, 156.4 (t, $^{2}J_{C,F}$ = 23.3 Hz), 157.2, 159.1, 162.0, 163.5, 192.4.

3-{[2-Methoxy-4-(trifluoromethyl)pyrimidin-5-yl]carbonyl}-4,6-dimethylpyridin-2(1*H*)-one (10b)

This compound was prepared from azachromone **9** (R^F = CF_3) and *O*-methylurea in an analogous manner to **10a**; yield: 124 mg (38%); yellow crystals; mp 217–218 °C.

IR (KBr): 3000–2660, 1670, 1656, 1624, 1584, 1550, 1537, 1479 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.98 (d, *J* = 0.5 Hz, 3 H, 6-Me), 2.46 (s, 3 H, 4-Me), 4.09 (s, 3 H, MeO), 6.06 (s, 1 H, H-5′), 8.63 (s, 1 H, H-6), 12.98 (s, 1 H, NH).

Compounds 11a–d; General Procedure

A soln of chromone **1** (1.0 mmol) and sulfaguanidine (220 mg, 1.03 mmol) in EtOH (10 mL) was refluxed for 3 h and then left at r.t. for 2 d. The precipitate that formed was filtered off, washed with EtOH, and recrystallized (EtOH) to give pure product **11** as yellow crystals.

***N*-Carbamimidoyl-4-({[2-hydroxy-4-oxo-2-(trifluoromethyl)-2*H*-chromen-3(4*H*)-ylidene]methyl}amino)benzenesulfonamide (11a)**

Yield: 255 mg (77%); mp 210–212 °C.

IR (KBr): 3460, 3412, 3367, 3227, 1646, 1617, 1596, 1550, 1470 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 6.72 (br s, 4 H, 4NH), 7.08 (d, ^{3}J = 8.3 Hz, 1 H, H-8), 7.16 (ddd, ^{3}J = 7.9, 7.2 Hz, ^{4}J = 0.8 Hz, 1 H, H-6), 7.52–7.55 (m, 2 H, Ar), 7.57 (ddd, ^{3}J = 8.4, 7.3 Hz, ^{4}J = 1.7 Hz, 1 H, H-7), 7.76–7.79 (m, 2 H, Ar), 7.84 (dd, ^{3}J = 7.8 Hz, ^{4}J = 1.6 Hz, 1 H, H-5), 8.04 (d, *J* = 12.7 Hz, 1 H, = CH), 9.19 (s, 1 H, OH), 12.51 (d, *J* = 12.7 Hz, 1 H, NH).

***N*-Carbamimidoyl-4-({[2-hydroxy-6-methyl-4-oxo-2-(trifluoromethyl)-2*H*-chromen-3(4*H*)-ylidene]methyl}amino)benzenesulfonamide (11b)**

Yield: 340 mg (86%); mp 236–238 °C.

IR (KBr): 3449, 3423, 3367, 3332, 3232, 1642, 1622, 1594, 1547, 1535, 1490, 1462 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 2.31 (s, 3 H, Me), 6.71 (br s, 4 H, 4NH), 6.98 (d, ^{3}J = 8.3 Hz, 1 H, H-8), 7.37 (ddq, ^{3}J = 8.3 Hz, ^{4}J = 2.3, 0.6 Hz, 1 H, H-7), 7.50–7.54 (m, 2 H, Ar), 7.62 (d, ^{4}J = 2.3 Hz, 1 H, H-5), 7.75–7.79 (m, 2 H, Ar), 8.02 (d, *J* = 12.7 Hz, 1 H, = CH), 9.12 (s, 1 H, OH), 12.49 (d, *J* = 12.7 Hz, 1 H, NH).

^{19}F NMR (DMSO-d_6): δ = –84.9 (s, CF_3).

***N*-Carbamimidoyl-4-({[2-(difluoromethyl)-2-hydroxy-4-oxo-2*H*-chromen-3(4*H*)-ylidene]methyl}amino)benzenesulfonamide (11c)**

Yield: 265 mg (74%); mp 174–176 °C.

IR (KBr): 3457, 3425, 3363, 3220, 1643, 1610, 1596, 1544, 1469 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 6.10 (t, $^{2}J_{H,F}$ = 55.3 Hz, 1 H, CF_2H), 6.71 (br s, 4 H, 4NH), 7.02 (dd, ^{3}J = 8.3 Hz, ^{4}J = 0.9 Hz, 1 H, H-8), 7.10 (ddd, ^{3}J = 7.9, 7.2 Hz, ^{4}J = 1.0 Hz, 1 H, H-6), 7.47–7.51 (m, 2 H, Ar), 7.53 (ddd, ^{3}J = 8.4, 7.2 Hz, ^{4}J = 1.7 Hz, 1 H, H-7), 7.75–7.79 (m, 2 H, Ar), 7.81 (dd, ^{3}J = 7.8 Hz, ^{4}J = 1.7 Hz, 1 H, H-5), 7.94 (d, *J* = 12.6 Hz, 1 H, = CH), 8.46 (s, 1 H, OH), 12.47 (d, *J* = 12.6 Hz, 1 H, NH).

***N*-Carbamimidoyl-4-({[2-hydroxy-4-oxo-2-(1,1,2,2-tetrafluoroethyl)-2*H*-chromen-3(4*H*)-ylidene]methyl}amino)benzenesulfonamide (11d)**

Yield: 284 mg (72%); mp 212–213 °C.

IR (KBr): 3456, 3370, 3333, 3227, 1646, 1611, 1594, 1533, 1470 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 6.72 (tdd, $^{2}J_{H,F}$ = 52.0 Hz, $^{3}J_{H,F}$ = 7.9, 5.1 Hz, 1 H, CF_2CF_2H), 6.72 (br s, 4 H, 4NH), 7.02 (dd, ^{3}J = 8.3 Hz, ^{4}J = 0.8 Hz, 1 H, H-8), 7.13 (ddd, ^{3}J = 7.9, 7.3 Hz, ^{4}J = 1.0 Hz, 1 H, H-6), 7.50–7.54 (m, 2 H, Ar), 7.55 (ddd, ^{3}J = 8.3, 7.3 Hz, ^{4}J = 1.7 Hz, 1 H, H-7), 7.76–7.80 (m, 2 H, Ar), 7.82 (dd, ^{3}J = 7.8 Hz, ^{4}J = 1.7 Hz, 1 H, H-5), 7.96 (dd, *J* = 12.7, $^{5}J_{H,F}$ = 1.0 Hz, 1 H, = CH), 9.10 (d, $^{4}J_{H,F}$ = 4.0 Hz, 1 H, OH), 12.49 (d, *J* = 12.7 Hz, 1 H, NH).

2-Hydroxy-3-[(2-hydroxyphenylamino)methylene]-2-(trifluoromethyl)chroman-4-one (11e)

Yield: 309 mg (88%); mp 172–174 °C; R_f = 0.37 (PE–EtOAc, 2:1).

^{1}H NMR (DMSO-d_6): δ = 6.84 (t, ^{3}J = 7.6 Hz, 1 H), 6.90–6.98 (m, 2 H), 7.01 (d, ^{3}J = 7.6 Hz, 1 H), 7.09 (t, ^{3}J = 7.6 Hz, 1 H), 7.39 (d, ^{3}J = 7.6 Hz, 1 H), 7.48 (t, ^{3}J = 7.6 Hz, 1 H), 7.79 (d, ^{3}J = 7.6 Hz, 1 H), 8.01 (d, *J* = 13.2 Hz, 1 H, = CH), 9.01 (s, 1 H), 10.37 (s, 1 H), 12.69 (d, *J* = 13.2 Hz, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 98.0 (q, $^{2}J_{C,F}$ = 33 Hz), 98.8, 114.8, 115.8, 116.5, 122.2, 122.9 (q, $^{1}J_{C,F}$ = 289 Hz), 125.3, 125.7, 127.4, 139.8, 145.9, 146.6, 155.7, 179.2.

^{19}F NMR (DMSO-d_6): δ = –85.3.

MS (EI, 70 eV): *m/z* (%) = 351 (34) $[M]^+$, 283 (27) $[M + 1 – CF_3]^+$, 282 (100) $[M – CF_3]^+$, 243 (15) $[M – C_6H_6NO]^+$, 173 (31) $[C_{10}H_5O_3]^+$, 121 (54) $[HOC_6H_4CO]^+$, 120 (24) $[C_7H_6NO]^+$, 109 (45) $[C_6H_7NO]^+$, 65 (16).

Compounds 12a and 12b; General Procedure

A mixture of **5k** or **8d** (0.6 mmol), NaOH (120 mg, 3 mmol), K_2CO_3 (690 mg, 5 mmol), Bu_4NHSO_4 (72 mg, 0.2 mmol), and Me_2SO_4 (170 μL, 1.8 mmol) in toluene (10 mL) was stirred for 20 h under reflux. The solid phase was filtered off, the liquor was concentrated in vacuo, and the residue was purified by flash chromatography (silica gel).

5-(2-Methoxybenzoyl)-2-(morpholin-4-yl)-4-(trifluoromethyl)pyrimidine (12a)

Yield: 252 mg (77%); yellow oil; R_f = 0.52 (Et_2O).

^{1}H NMR ($CDCl_3$): δ = 3.66 (s, 3 H, MeO), 3.74 (t, ^{3}J = 4.7 Hz, 4 H, morpholino), 3.90 (t, ^{3}J = 4.7 Hz, 4 H, morpholino), 6.91 (d, ^{3}J = 8.5 Hz, 1 H, H-3′), 7.01 (td, ^{3}J = 7.6 Hz, ^{4}J = 0.9 Hz, 1 H, H-5′), 7.48 (ddd, ^{3}J = 8.5, 7.0 Hz, ^{4}J = 1.8 Hz, 1 H, H-4′), 7.61 (dd, ^{3}J = 7.6 Hz, ^{4}J = 1.8 Hz, 1 H, H-6′), 8.37 (s, 1 H, H-6).

^{13}C NMR ($CDCl_3$): δ = 44.1, 55.5 (q, $J_{C,F}$ = 2.6 Hz), 66.5, 111.6 (q, $J_{C,F}$ = 1.6 Hz), 120.3 (q, $^{1}J_{C,F}$ = 277.0 Hz), 120.8, 121.4, 127.1, 131.3, 153.8 (q, $^{2}J_{C,F}$ = 36.0 Hz), 134.4, 158.5, 160.4, 161.1, 191.1.

MS (EI, 70 eV): *m/z* (%) = 367 (100) $[M]^+$, 299 (10) $[M + 1 – CF_3]^+$, 298 (34) $[M – CF_3]^+$, 261 (23), 260 (89), 234 (73), 233 (44), 136 (19), 135 (55), 112 (11), 111 (12).

5-(2-Methylsulfanylbenzoyl)-2-morpholino-4-(trifluoromethyl)pyrimidine (12b)

Yield: 268 mg (70%); yellow oil; R_f = 0.65 (Et_2O).

^{1}H NMR ($CDCl_3$): δ = 2.55 (s, 3 H, MeS), 3.70 (t, ^{3}J = 4.7 Hz, 4 H, morpholino), 4.07 (t, ^{3}J = 4.7 Hz, 4 H, morpholino), 7.49–7.66 (m, 3 H, H-3′, H-4′, H-5′), 7.99 (d, ^{3}J = 7.8 Hz, 1 H, H-6′), 8.81 (s, 1 H, H-6).

^{13}C NMR ($CDCl_3$): δ = 25.0 (q, $J_{C,F}$ = 2.2 Hz), 42.3, 68.1, 112.0 (q, $J_{C,F}$ = 1.6 Hz), 120.2 (q, $^1J_{C,F}$ = 277.0 Hz), 122.2, 122.4, 129.7, 135.0, 137.4, 153.8 (q, $^2J_{C,F}$ = 36.0 Hz), 159.3, 162.0, 163.1, 191.1.

MS (EI, 70 eV): *m/z* (%) = 383 (100) $[M]^+$, 315(89) $[M + 1 - CF_3]^+$, 314 (14) $[M - CF_3]^+$.

Ethyl (2-{[2-(Morpholin-4-yl)-4-(trifluoromethyl)pyrimidin-5-yl]carbonyl}phenoxy)acetate (13)

A mixture of **5k** (353 mg, 1 mmol), K_2CO_3 (690 mg, 5 mmol), and $BrCH_2CO_2Et$ (175 μL, 1.5 mmol) in acetone (20 mL) was stirred at r.t. overnight. The solid phase was filtered off and the liquor was concentrated in vacuo providing the pure white crystalline product; yield: 426 mg (97%); mp 150–153 °C.

^{1}H NMR ($CDCl_3$): δ = 1.20 (t, ^3J = 7.1 Hz, 3 H, Me), 3.75 (dd, ^3J = 5.1, 4.6 Hz, 4 H, morpholino), 3.91 (dd, ^3J = 5.1, 4.6 Hz, 4 H, morpholino), 4.13 (q, ^3J = 7.1 Hz, 2 H, OCH_2), 4.47 (s, 2 H, CH_2), 7.08 (d, ^3J = 7.7 Hz, 1 H, H-3′), 7.10 (t, ^3J = 7.7 Hz, 1 H, H-5′), 7.48 (td, ^3J = 7.7 Hz, ^4J = 1.7 Hz, 1 H, H-4′), 7.67 (dd, ^3J = 7.7 Hz, ^4J = 1.7 Hz, 1 H, H-6′), 8.47 (s, 1 H, H-6).

^{13}C NMR ($CDCl_3$): δ = 13.9, 44.3, 61.3, 65.4, 66.6, 112.2, 120.4 (q, $^1J_{C,F}$ = 277.0 Hz), 122.0, 127.89, 131.6, 134.2, 153.8 (q, $^2J_{C,F}$ = 36.0 Hz), 156.5, 160.6, 161.4, 167.7, 190.9.

MS (EI, 70 eV): *m/z* (%) = 439 (11) $[M]^+$, 370 (57), 260 (71), 232 (100).

4-[5-(1-Benzofuran-3-yl)-4-(trifluoromethyl)pyrimidin-2-yl]morpholine (14)

Glacial AcOH (30 mL) was added to a mixture of KCl (1.37 g) and **15**, prepared from **13** (0.88 g, 2 mmol) (see below). The resulting mixture was refluxed for 24 h then concentrated in vacuo. The residue was purified by flash chromatography (PE–Et_2O, 2:1) to give **14** as a colorless crystals; yield: 620 mg (89%); mp 125–129 °C; R_f = 0.45.

^{1}H NMR ($CDCl_3$): δ = 3.79 (dd, ^3J = 5.2, 4.4 Hz, 4 H, morpholino) 3.91 (dd, ^3J = 5.2, 4.4 Hz, 4 H, morpholino), 7.26 (t, ^3J = 7.8 Hz, 1 H, H-5′), 7.35 (td, ^3J = 7.8 Hz, ^4J = 1.2 Hz, 1 H, H-6′), 7.40 (dd, ^3J = 7.8 Hz, ^4J = 1.2 Hz, 1 H, H-4′), 7.54 (d, ^3J = 7.8 Hz, 1 H, H-7′), 7.63 (s, 1 H, H-2′), 8.50 (s, 1 H, H-6).

^{13}C NMR ($CDCl_3$): δ = 44.2, 66.7, 110.3, 111.8, 114.2, 119.7, 120.9 (q, $^1J_{C,F}$ = 277.0 Hz), 123.2, 124.9, 127.9, 143.5 (q, $J_{C,F}$ = 2.4 Hz), 154.0 (q, $^2J_{C,F}$ = 34.0 Hz), 155.0, 160.5 (q, $^4J_{C,F}$ = 1.0 Hz), 162.3.

MS (EI, 70 eV): *m/z* (%) = 350 (14) $[M + 1]^+$, 349 (100) $[M]^+$, 281 (19) $[M + 1 - CF_3]^+$, 280$^+$ (98) $[M - CF_3]$], 232 (75) $[M - C_8H_5O]^+$.

3-Hydroxy-3-[2-(morpholin-4-yl)-4-(trifluoromethyl)pyrimidin-5-yl]-2,3-dihydro-1-benzofuran-2-carboxylic Acid (15)

A mixture of **13** (415 mg, 0.95 mmol) and KOH (265 mg, 4.73 mmol) in dioxane (20 mL) was stirred for 1 h at 30 °C to give a red soln to which was added 2 M aq HCl (2.37 mL). The resulting soln was concentrated in vacuo to give a gray solid residue (760 mg) consisting of the expected product and KCl. This mixture was used for the synthesis of **14** without further purification.

Yield: 383 mg (98%); mp 172–175 °C.

^{1}H NMR (DMSO-d_6): δ = 3.66 (dd, ^3J = 5.1, 4.6 Hz, 4 H, morpholino), 3.72 (dd, ^3J = 5.1, 4.6 Hz, 4 H, morpholino), 4.53 (s, 1 H, CH), 6.81 (d, ^3J = 7.7 Hz, 1 H, H-4′), 6.83 (t, ^3J = 7.7 Hz, 1 H, H-5′), 6.97 (d, ^3J = 7.7 Hz, 1 H, H-7′), 7.19 (t, ^3J = 7.7 Hz, 1 H, H-6′), 8.48 (s, 1 H, H-6), 9.69 (s, 1 H, OH).

^{13}C NMR (DMSO-d_6): δ = 43.7, 65.6, 78.6, 88.8, 109.3, 120.2, 120.6 (q, $^1J_{C,F}$ = 276.0 Hz), 124.4, 129.1, 133.5, 151.4 (q, $^2J_{C,F}$ = 34.0 Hz), 159.6 (q, $^4J_{C,F}$ = 1.2 Hz), 159.4, 161.0, 169.6 (q, $J_{C,F}$ = 7.0 Hz).

MS (EI, 70 eV): *m/z* (%) = 411 (10) $[M]^+$, 393 (83) $[M - H_2O]^+$, 392 (59) $[M - 1 - H_2O]^+$, 349 (100) $[M - H_2O - CO_2]^+$, 348 (11) $[M - 1 - H_2O - CO_2]^+$, 281 (11) $[M + 1 - H_2O - CO_2 - CF_3]^+$, 280 (37) $[M - H_2O - CO_2 - CF_3]^+$, 232 (21) $[M - H_2O - CO_2 - C_8H_5O]^+$.

Compounds 16a–c; General Procedure

A soln of **5** (0.81 mmol) in THF (5 mL) was added dropwise to a stirred suspension of NaH (60% dispersion in mineral oil, 43 mg, 1.08 mmol) in dry THF (10 mL). H_2O_2 (35% aq soln, 100 mg, 1.03 mmol) was added to the resulting soln, and the mixture was stirred for 4 d at r.t. The mixture was then adjusted to pH ~4 with 1 M aq HCl and extracted with Et_2O. The combined organic layers were dried ($MgSO_4$), and the dissolved material was settled on silica gel. A grey crystalline product was obtained by flash chromatography with CH_2Cl_2, Et_2O, and MeOH sequentially.

Sodium 2-Methyl-4-(trifluoromethyl)pyrimidine-5-carboxylate (16a)

Yield: 138 mg (75%); mp 157–158 °C; R_f = 0.55 (MeOH).

^{1}H NMR (DMSO-d_6): δ = 2.64 (s, 3 H, Me), 8.84 (s, 1 H, H-6).

^{13}C NMR (DMSO-d_6): δ = 24.8, 120.9 (q, $^1J_{C,F}$ = 276.0 Hz), 131.0 (q, $^3J_{C,F}$ = 0.8 Hz), 148.4 (q, $^2J_{C,F}$ = 35.0 Hz), 159.1, 165.2.

MS (EI, 70 eV): *m/z* (%) = 228 (100) $[M]^+$, 161 (77).

Sodium 2-(Morpholin-4-yl)-4-(trifluoromethyl)pyrimidine-5-carboxylate(16b)

Yield: 194 mg (80%); mp 181–183 °C; R_f = 0.35 (MeOH).

^{1}H NMR (DMSO-d_6): δ = 3.64 (dd, ^3J = 5.0, 4.5 Hz, 4 H, morpholino), 3.69 (dd, ^3J = 5.0, 4.5 Hz, 4 H, morpholino), 8.70 (s, 1 H, H-6).

^{13}C NMR (DMSO-d_6): δ = 43.8, 65.6, 120.8 (q, $^1J_{C,F}$ = 277.0 Hz), 120.9 (q, $^3J_{C,F}$ = 2.0 Hz), 151.1 (q, $^2J_{C,F}$ = 34.0 Hz), 159.7, 162.1, 168.6.

MS (EI, 70 eV): *m/z* (%) = 299 (38) $[M]^+$, 232 (100).

Sodium 2-Methyl-4-(perfluoropropyl)pyrimidine-5-carboxylate (16c)

Yield: 207 mg (78%); mp 111–113 °C; R_f = 0.85 (MeOH).

^{1}H NMR (DMSO-d_6): δ = 2.79 (s, 3 H, Me), 9.01 (s, 1 H, H-6).

^{13}C NMR (DMSO-d_6): δ = 26.1, 108.9 (tqt, $^1J_{C,F}$ = 269.0 Hz, $^2J_{C,F}$ = 38.0, 36.0 Hz), 112.7 (tt, $^1J_{C,F}$ = 260.0 Hz, $^2J_{C,F}$ = 32.0 Hz), 117.0 (ttq, $^1J_{C,F}$ = 288.0 Hz, $^2J_{C,F}$ = 34.0 Hz, $^3J_{C,F}$ = 1.2 Hz), 132.3 (q, $^3J_{C,F}$ = 1.3 Hz), 151.4 (q, $^2J_{C,F}$ = 27.0 Hz), 159.1, 165.2.

MS (EI, 70 eV): *m/z* (%) = 328 (23) [M$^+$], 261 (85), 144 (14), 143 (100).

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